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THE EFFECT OF CHANGES IN CONCENTRATION OF CATIONS ON THE ELECTROCARDIOGRAM OF THE ISOLATED PERFUSED HEART*

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THE primary purpose of this study was to analyze the changes in the electrocardiogram of the isolated perfused heart which attend alterations in the concentration of potassium in the perfusate. In addition, the physiologic antagonism of calcium and potassium, and of sodium and potassium, as might be revealed by the cardiac potentials, was investigated.

The electrocardiogram has rarely been used in studying the effects of potassium on the isolated perfused heart.[1] Although electrical activity has been recorded from an electrode on the surface of the ventricle in the intact animal as the concentration of serum potassium was altered,[2-5] simultaneous cavity (endocardial) and surface (epicardial) ventricular electrodes have apparently not been utilized.

By an analysis of electrocardiograms recorded simultaneously from electrodes placed in the cavity and on the surface of the left ventricle, it was hoped to derive additional information in regard to the spread of excitation through the wall of the ventricle and the nature of intraventricular conduction defects as the concentration of potassium and other cations in the perfusate was altered.

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PROCEDURE

Approximately 100 turtle hearts (*Chelydra serpentina*) and thirty-eight dog hearts were used in this study.

The turtle heart with pericardium intact was prepared so that the entire organ could be perfused. The inflow cannula, which was connected to a small reservoir, was inserted into the right cardinal vein; oxygenated solutions at a constant temperature (25°C.) flowed successively into the sinus venosus, the right atrium, and the single ventricle, and escaped through the valves of the aortas and the pulmonary artery. An insulated, pliable copper wire scraped at the tip and covered with cotton was used as the electrode; it was inserted into the cavity of the ventricle by way of the sinus venosus and right atrium. Another cotton-tipped electrode was placed, through a small slit in the parietal pericardium, against the epicardium of the ventricle near the frenum. Both electrodes were attached to the leads of a Sanborn Tribeam Stethocardiette. The tip of the indifferent electrode was placed in the fluid of the reservoir. Perfusing solutions were freshly prepared each day with triple distilled water. The (standard) perfusate contained Na^+ 141.5, K^+ 3.27, Ca^{++} 5.46, HCO_3^- 4.4, Mg^{++} 2.37, and Cl^- 157.0 milliequivalents per liter.

The dog heart with pericardium intact was perfused by use of the Langendorff procedure with Tyrode's solution at a constant temperature of 39°C. Electrodes similar to those described in the preceding paragraph were used. One electrode was inserted by way of a pulmonary vein through the left atrium and mitral orifice into the cavity of the left ventricle. A 4 cm. length of rubber tubing of small diameter and with holes in its sides surrounded the electrode proximal to the exposed tip in order to render the mitral valve incompetent, so that the fluid entering the cavity of the left ventricle was easily ejected during systole retrogradely through the inflow tract of the left ventricle. The tip of the other electrode was placed through a small slit within the parietal pericardium, against the epicardium of the left ventricle. The two electrodes were connected to the leads of the electrocardiograph so that action potentials from the cavity and the surface of the left ventricle were recorded simultaneously. The pericardium overlying the apex of the heart lightly touched the flat bottom of a glass receptacle containing a small amount of the perfusate. The tip of the indifferent electrode was immersed in the perfusate in the container approximately 12 cm. from the apex of the heart.

RESULTS

In all the experiments in which the concentration of cations was altered, the exact isotonicity and pH of the standard solution were not maintained. Disregard of these factors seemed justified in that it was shown that addition to or subtraction from the standard perfusate of 34 meq. of sodium per liter and 34 meq. of chloride per liter (sodium chloride) had little or no effect on the electrocardiogram. The osmotic changes produced by altering the concentrations of the various ions during any experiment were far less than that produced by the change of 34 meq. of sodium and of chloride per liter, except in the few experiments in which sodium chloride was absent from the perfusate.

No changes in the electrocardiogram were noted when the pH of the perfusate was altered from the usual pH of approximately 8.0 to a pH of 7.5 or 8.5. During all experiments the pH of the perfusate was within the range of 7.5 and 8.5 in spite of alterations in the concentrations of the various ions in the perfusate.

Variations of the T waves in the control electrocardiograms of both the isolated turtle and dog hearts frequently occurred; the simultaneous occurrence of either upright T waves in the tracings from both the cavity and the epicardial leads or inverted T waves in both of these tracings was occasionally observed (Figs. 1 and 5,*b*).

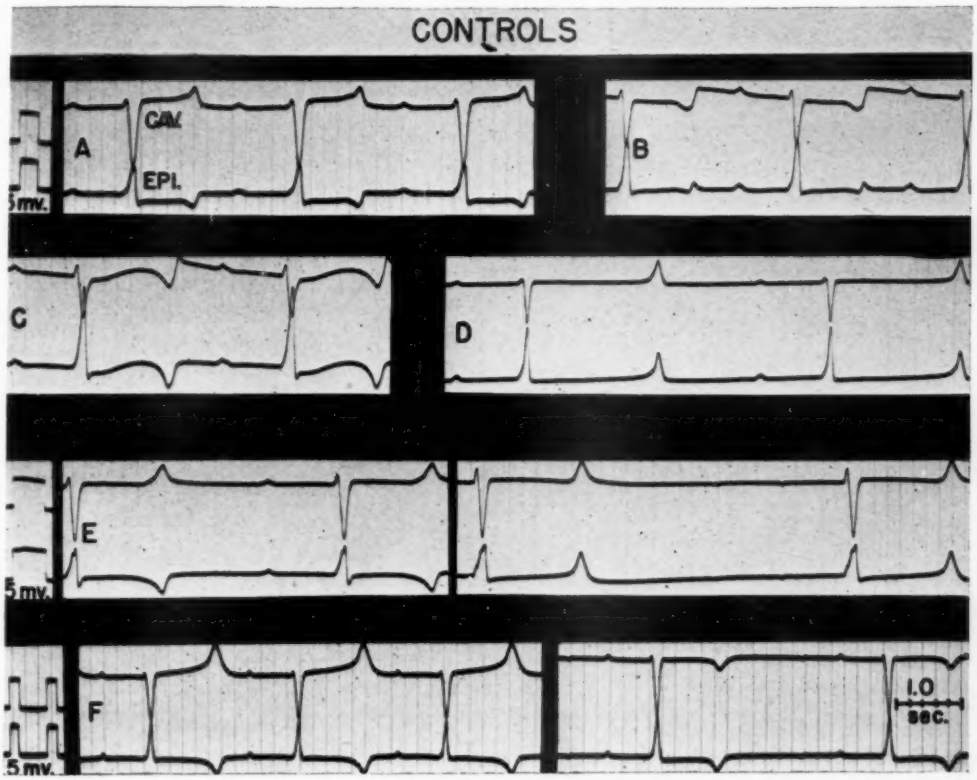


Fig. 1.—Turtle heart. Control electrocardiograms, showing unusual changes in T wave and S-T segment. Standard deflection is 5 millivolts. *CAV.*, Electrocardiogram from electrode in the ventricular cavity; *EPI.*, electrocardiogram from electrode on the epicardial surface of the ventricle.

A, Control electrocardiogram at the beginning of an experiment, showing the configuration of the P waves, QRS complexes, and T waves seen in the majority of the experiments.

B, Control electrocardiogram at the beginning of an experiment, showing inverted T waves in the tracing from the cavity lead, and depression of the S-T segment in the tracing from the cavity lead without reciprocal elevation in the tracing from the epicardial lead.

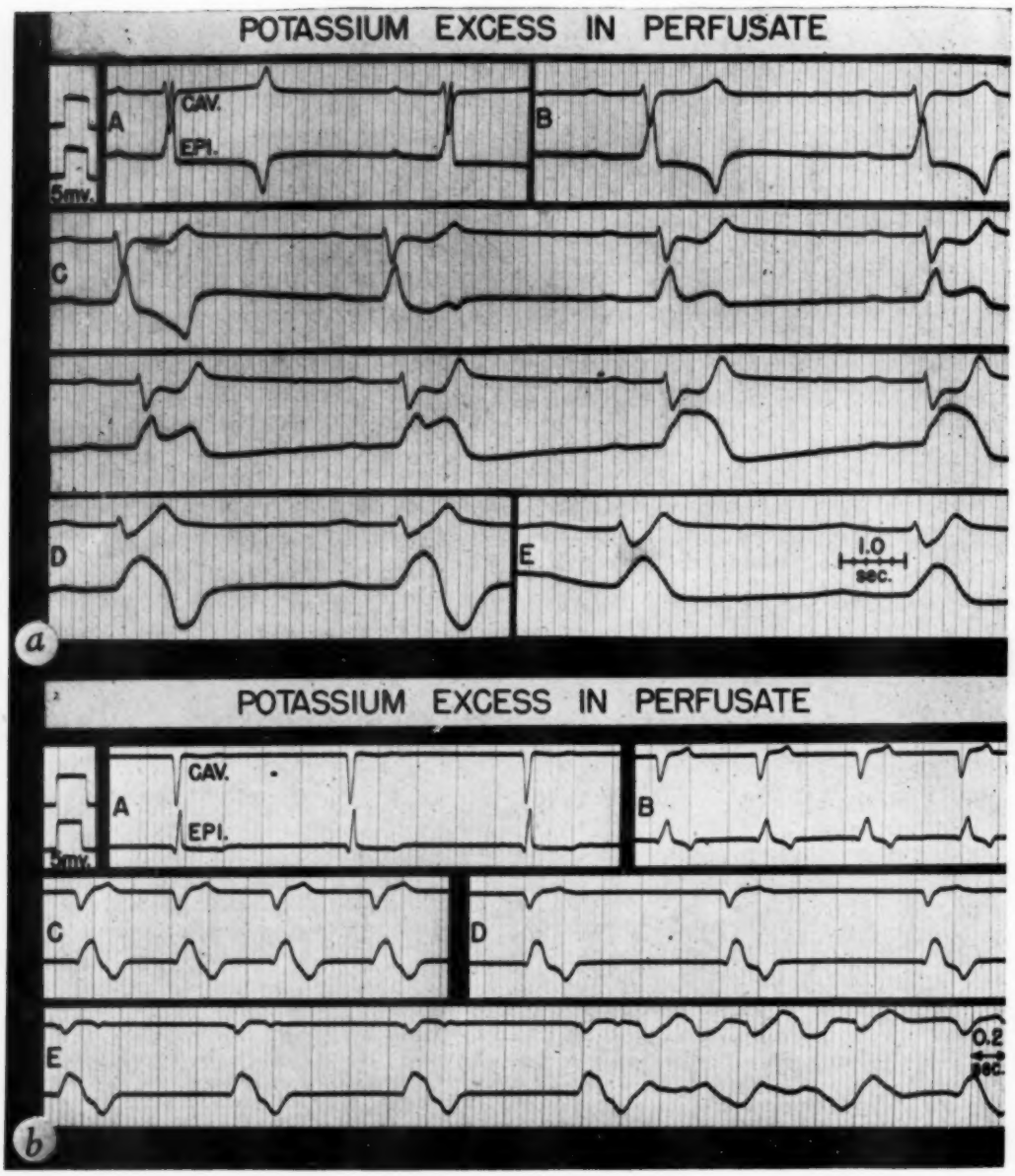
C, Control electrocardiogram at the beginning of an experiment, showing inversion of the main deflection of the T waves in both tracings and depression of the S-T segment take-off in both tracings.

D, Control electrocardiogram at the beginning of an experiment, showing upright T waves in both tracings.

E, Control experiment. First record is the initial control tracing. Second record is the tracing after four hours of perfusion with the standard solution (note upright T waves in tracings from both cavity and epicardial leads).

F, Control experiment. First record is the initial control tracing. Second record is the tracing after five hours of perfusion with the standard solution (note inverted T waves in tracings from both cavity and epicardial leads).

a.



b.

Fig. 2.—*a*, Turtle heart. Effects of an excess of potassium in the perfusate. Standard deflection is 5 millivolts. *CAV.*, Electrocardiogram from electrode in the ventricular cavity; *EPI.*, electrocardiogram from electrode on the epicardial surface of the ventricle. *A*, Control. *B*, After two minutes of perfusion with the solution containing an excess of potassium (9.81 meq. per liter). *C*, After two and one-half minutes, showing eight consecutive complexes. *D*, After four minutes. *E*, After ten minutes.

b, Dog heart. *A*, Control (2:1 block). *B*, After one minute of perfusion with a Tyrode solution containing an excess of potassium (12.02 meq. per liter). Still 2:1 block. *C*, After one and three-fourths minutes (no P waves). *D*, After two minutes. *E*, After three minutes (the slow, undulating waves at the end were followed by complexes similar to the first three complexes in *E*).

ELECTROCARDIOGRAPHIC CHANGES PRODUCED BY EXCESS OF POTASSIUM IN PERFUSATE

Procedure.—After control records had been established, the hearts were perfused with the same standard solution, to which an excess of potassium chloride had been added.

Results.—In the electrocardiograms of the turtle hearts, changes developed when the concentration of potassium in the perfusate was 7.0 meq. or more per liter. In the electrocardiograms of the dog hearts, changes developed when the concentration of potassium was 10 meq. or more per liter. The degree of change in the electrocardiogram not only varied with the concentration of potassium in the perfusate but also varied between hearts which were perfused with the same concentration of potassium.

The effects of an excess of potassium in the perfusate on the turtle and dog hearts were basically similar. However, the atria and sinus venosus of the turtle heart were more tolerant to an excess of potassium than was the ventricle; broad P waves continued to appear after ventricular arrest had taken place. In contrast, the atria of the dog heart stopped before the ventricles, and their electrical components (P waves) were the first to disappear from the electrocardiogram (Fig. 2,*b*).

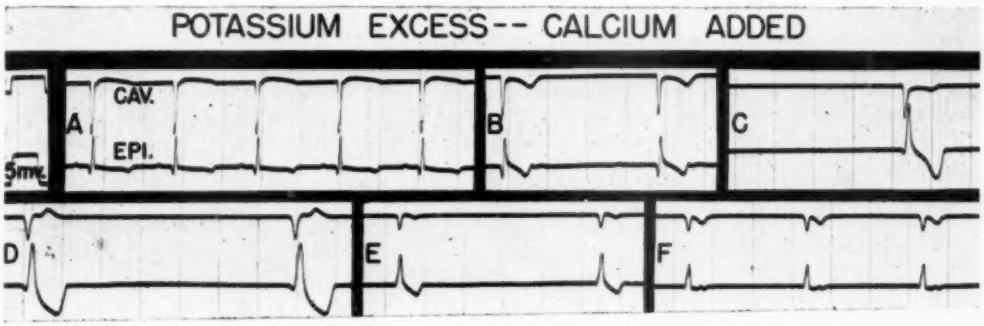


Fig. 3.—Dog heart. Electrocardiographic changes produced by adding extra calcium to the perfusate when heart was under the influence of an excess of potassium in the perfusate. *CAV.*, Electrocardiogram from electrode in the cavity of the left ventricle; *EPI.*, electrocardiogram from electrode on the epicardial surface of the left ventricle. *A*, Control. Note inverted T waves in both tracings. *B*, After thirty seconds of perfusion with a Tyrode solution containing an excess of potassium (12.02 meq. per liter). Note 2:1 block. Transient (about twenty seconds' duration) cardiac arrest occurred after one minute. *C*, After two minutes. Note absence of P waves. *D*, After five minutes. *E* and *F*, After thirty seconds and three minutes, respectively, of perfusion with a solution containing not only 12.02 meq. of potassium per liter but also 16.2 meq. of calcium per liter, about four times the usual concentrations of both potassium and calcium in the control perfusate.

The changes in the components of electrical activity can be listed in their usual order of appearance (Figs. 2,*a*, 2,*b*, and 3):

1. The amplitude of the QRS complex decreased.
2. The S-T interval shortened.
3. The amplitude of the T wave usually increased. The width of the T wave increased or remained the same.
4. In the tracings of the turtle heart the P waves became broad and flat and the P-R interval was prolonged. In the tracings from the dog heart the P waves flattened early and completely disappeared.
5. There was a progressive increase in the QRS interval.
6. Variable S-T segment displacement occurred. In the records of the turtle heart, there was usually a depressed take-off of the S-T segment in the tracings from the cavity lead, but variable depression and elevation of the S-T segment take-off occurred in the tracings from the epicardial lead. Reciprocal changes in the two tracings were not always present (Fig. 2,*a*).

In the records of the dog heart, the S-T segment (or take-off) in the tracings from the cavity lead, elevated during the control period in seven of the nine records, became more elevated in one (Fig. 2,*b*), isoelectric in three (one of which later became elevated), and depressed in three (one of which later became elevated). The S-T segment, depressed during the control period in the other two of the nine records, remained depressed in one and became elevated in the other record.

In the tracings from the epicardial lead of the dog heart the S-T segment, which was depressed during the control period in seven of the nine records, became more depressed in two (Fig. 2,*b*), isoelectric in one, and elevated in four (two of which later became depressed). The S-T segment, which was elevated slightly during the control period in the other two of the nine records, became more elevated in one and depressed in the other record.

A reciprocal relationship between the S-T segment in the tracings from the cavity lead and the S-T segment in the tracings from the epicardial lead was not observed in four of the nine records.

7. There was a decrease in ventricular rate. Partial or complete atrioventricular dissociation occurred in the records of the turtle hearts. In three of the nine records of the dog hearts, there was an early transient period (fifteen to thirty seconds) of ventricular arrest shortly after the P waves had disappeared (Fig. 3). The ventricle then resumed activity at a slow rate (less than one-half the control rate). In two records ventricular arrest occurred early with little change in rate prior to arrest; the ventricle did not resume activity.

8. Wide diphasic forms or monophasic forms developed so that there was not a clear separation between the various components of electrical activity.

9. Complete cessation of electrical activity of the ventricle finally occurred. The ventricle stopped in diastole. In one of the electrocardiograms of a dog heart ventricular fibrillation, characterized by undulating potentials at a slow rate, developed after three minutes of perfusion (Fig. 2,*b*).

Comment.—Martin[6] and Howell,[7] nearly fifty years ago, observed that the atria and sinus venosus of the turtle heart were more tolerant to an excess of potassium than was the ventricle. Similar results were observed in our experiments. In contrast to the turtle atria the mechanical and electrical activity of the atria of the dog heart stopped before the ventricles. No instance was noted in which atrial activity persisted after ventricular activity had ceased as noted by Wiggers and associates[8] and Bellet and associates.[2]

The changes in the components of electrical activity noted in this study in the tracings from a lead on the epicardium of the left ventricle of the isolated dog heart perfused with an excess of potassium are generally in accord with those changes reported by others in tracings from a lead on the epicardium of the isolated perfused rabbit heart[1] and in tracings from leads on the precordium and from standard leads of the intact animal (dog and cat)[2,4,5,8-12] particularly in regard to delayed intraventricular conduction, increased amplitude of T waves, and wide, flat, or absent P waves.

The few differences that exist between the results of the present work and the observations reported by others are summarized in the following paragraphs.

Although the amplitude of the T waves was increased, the change was not as striking, as has been observed by others, in the intact animal[12] and in the isolated perfused heart of the rabbit.[1] In a few of our records the T waves recorded from both the epicardial lead and the cavity lead were in the same direction, and, rarely, an increase in the depth of the T wave in the tracing from the epicardial lead developed without an increase in the height of the T wave in the tracing from the cavity lead.

Depression of the S-T segment, reported by Winkler and associates[12] to occur in the tracings from epicardial leads of the canine heart in situ under the influence of an elevated serum potassium, was not a constant finding in our experiments; in fact, slight elevation of the segment was observed in one-third of our records. These findings are in accord with the report of Bellet and associates,[2] who found inconstant depression of the S-T segment in precordial leads. However, a reciprocal relationship between endocardial and epicardial potentials, reported by Bellet and associates[2] in one intact dog with hyperpotassemia, was observed in only about one-half of our records.

The changes in the electrocardiogram in the human being with hyperpotassemia are well documented in the literature and have recently been reviewed.[1,14] In general, the changes in the electrocardiogram of man with hyperpotassemia are similar to those found in the intact experimental animal.

An increase in the amplitude of the T wave and a depression of the S-T segment in the standard leads and precordial leads in both the experimental animal and man with hyperpotassemia have led to the supposition that a record of ventricular cavity potentials would show T waves opposite in direction to those in precordial leads, and elevation of the S-T segments. This possibility was enhanced by the finding of elevated S-T segments in Lead aV_R as opposed to the depressed S-T segments in precordial Leads V_{3-6} in man with hyperpotassemia.[15]

From such evidence the concept has arisen that an excess of potassium in blood acts like an injury to the endocardial surface of the ventricle.[15] The results of our experiments on isolated perfused turtle and dog hearts utilizing cavity and epicardial leads do not support this concept. Depressed S-T segments in the epicardial lead of either the turtle heart or the dog heart were not observed in all records. When depressed S-T segments in the epicardial lead were present, the S-T segments in the cavity lead were elevated, isoelectric, or depressed. In other words the cavity potential was not the reciprocal of the epicardial potential in all tracings.

A delay in intraventricular conduction has been known for many years to be one of the striking effects of potassium intoxication, but there has been some disagreement as to the exact nature and location of this delay. Some investigators believe that conduction is first delayed in the cells of the bundle branches, Purkinje network, and subendocardial fibers.[8,12,16] Others are of the opinion that the entire ventricle is affected by the potassium, simultaneously and indiscriminately, with a generalized delay in the spread of the wave of excitation.[15,17] The electrocardiograms in this study are interpreted as supporting the latter hypothesis.

ELECTROCARDIOGRAPHIC CHANGES PRODUCED BY ADDING EXTRA CALCIUM TO HEARTS UNDER INFLUENCE OF EXCESS OF POTASSIUM

Procedure.—Hearts were first subjected to a perfusate containing a concentration of potassium that would produce the electrocardiographic changes characteristic of an excess of potassium. After the typical changes had developed,

an excess of calcium was added to the perfusate so that the original ratio of potassium and calcium was restored but at a higher concentration of each.

Results (*Fig. 3*).—1. The ventricular rate, slow and frequently irregular from potassium excess alone, was increased moderately by the addition of calcium.

2. The prolonged QRS interval of potassium excess was shortened.
3. The short S-T interval of potassium excess was further shortened.
4. The final electrocardiograms did not resemble closely the control records.
5. Changes in the T waves were inconsistent and did not follow any definite pattern.

Comment.—The physiologic antagonism of calcium and potassium salts has been known since the observations of Ringer.[18] In studying the electrocardiographic effects of an excess of potassium on the isolated perfused rabbit heart, McLean and associates[1] reported that a simultaneous increase in the concentration of calcium and potassium did not alter the electrical changes characteristic of an excess of potassium. Winkler and associates[19] demonstrated in dogs that the lethal effect of injected potassium was diminished by the simultaneous administration of calcium. They also observed no electrocardiographic changes apart from those associated with the injection of potassium alone.

In the present study, however, the addition of extra calcium to a perfusate containing an excess of potassium lessened the delay in intraventricular conduction and further shortened the S-T interval produced by the excess of potassium.

EFFECT ON ELECTROCARDIOGRAM OF RESTORING LOW SODIUM CONCENTRATION TO NORMAL WHILE HEARTS WERE UNDER INFLUENCE OF PERFUSATE OF LOW SODIUM AND HIGH POTASSIUM CONTENT

Procedure.—Following a control record, hearts were perfused with a solution in which the sodium content was decreased (from 141.5 to 107.3 meq. per liter in the perfusate of the turtle hearts, and from 149 to 116 meq. per liter in the perfusate of the dog hearts). The potassium concentration in the perfusate was then increased until the electrocardiographic changes characteristic of potassium excess developed. Finally the sodium content was restored to the standard value.

Results.—In the electrocardiograms of the turtle heart, no changes occurred when the sodium concentration was decreased from 141.5 to 107.3 meq. per liter.

In the records of the dog heart, a decrease in the sodium content of the perfusate from 149 to 116 meq. per liter caused early electrocardiographic changes consisting of an increased rate, a shortened S-T interval, and an elevated epicardial and depressed cavity S-T segment. However, as perfusion was continued for five minutes or more, the heart rate, the S-T interval, and the segmental changes again approximated those of the control tracings (Fig. 4).

The concentration of potassium necessary to produce the electrocardiographic changes of potassium excess was less than when sodium was present in the standard amount. Restoration of the sodium content to the standard value partially reversed the electrocardiographic changes characteristic of an excess of potassium. It was also noted that decreasing the sodium content with the turtle heart already under the influence of an excess of potassium enhanced the electrocardiographic effects of the latter.

In a few experiments in which the turtle heart was first subjected to a perfusate containing an excess of potassium and then the sodium content was increased from the standard concentration

of 141.5 meq. per liter to 158.6 or 175.5 meq. per liter, the changes in the components of electrical activity characteristic of an excess of potassium were partially but not markedly reversed.

Comment.—The fact that sodium will counteract the effects of potassium in the experimental animal also has been known for many years.[20,21] No report was found in which this physiologic antagonism had been studied electrocardiographically in either the intact animal or the isolated heart. However there are several articles in the clinical literature which mention the role of low serum sodium in the aggravation of the clinical status of acute potassium intoxication.[14,17,22,23]

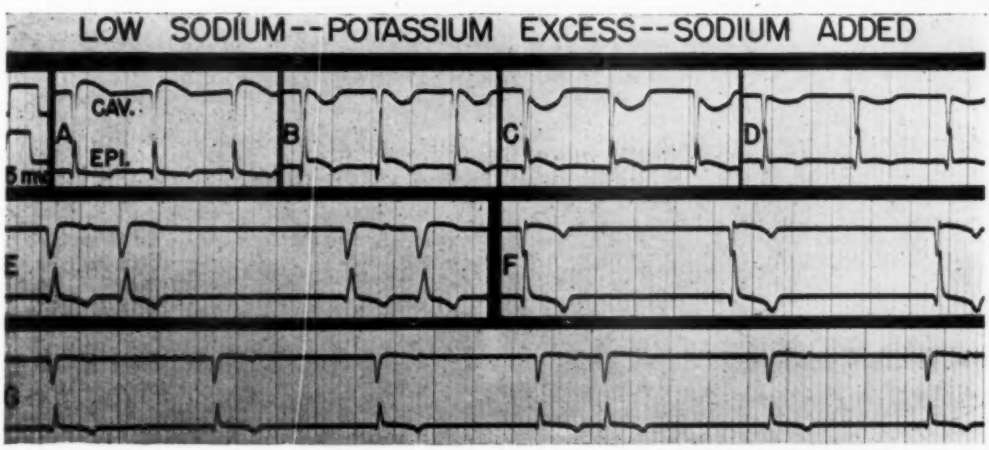


Fig. 4.—Dog heart. Effect on the electrocardiogram of restoring a low sodium concentration to normal while the heart was under the influence of a perfusate having a low sodium and a high potassium content. *CAV.*, Electrocardiogram from electrode in the cavity of the left ventricle; *EPI.*, electrocardiogram from electrode on the epicardial surface of the left ventricle. *A*, Control. *B*, *C*, and *D*, After three, five, and seven minutes, respectively, of perfusion with a solution having a low sodium content (decreased from 149 to 116 meq. per liter) . *E*, After five minutes of perfusion with a solution having a low sodium content (116 meq. per liter) and an excess of potassium (8 meq. per liter). *F* and *G*, After thirty seconds and four minutes, respectively, of perfusion with a solution having an excess of potassium (8 meq. per liter) and 149 meq. of sodium per liter.

The electrocardiograms in our studies on both turtle and dog hearts indicate that the administration of a sodium salt would at least partially reverse the electrocardiographic changes attributed to an elevated potassium concentration, particularly if a sodium deficiency also existed.

The clinical use of hypertonic solution of sodium chloride in the treatment of acute potassium intoxication has been reported with variable results.[14,17,22-24] However, an infusion of sodium is reported to be of benefit in those cases in which sodium depletion has been a factor in the production of potassium intoxication.[14,17,22]

ELECTROCARDIOGRAPHIC CHANGES PRODUCED BY ABSENCE OF POTASSIUM FROM PERFUSATE

Procedure.—After control records had been established, hearts were perfused with a solution containing the standard concentrations of electrolytes with the exception of a complete absence of potassium chloride.

Results (Fig. 5,*a* and *b*).—1. The S-T interval and the width of the T wave were increased almost immediately on exposure of the ventricle to the potassium-free perfusate. As perfusion continued, the distal limb of the broad T wave engulfed the next P wave (if present). The S-T interval was prolonged in the presence of a ventricular rate equal to or faster than the control rate.

2. In the records of the turtle hearts, the QRS interval was prolonged prior to partial or complete atrioventricular dissociation. In the records of the dog hearts, however, there was no or only a slight increase in the QRS interval before atrioventricular dissociation occurred.

3. The P-R interval increased prior to the development of complete atrioventricular dissociation.

4. Ventricular fibrillation developed within ten minutes in the records of the dog hearts. However, in the records of the turtle hearts, the ventricle continued to beat irregularly after an hour, or ventricular fibrillation developed, or electrical activity ceased as the ventricle stopped midway between systolic and diastolic positions.

Comment.—Since Janota and Weber[25] reported electrocardiographic alterations in a patient with familial periodic paralysis, and Stewart and associates[26] in a similar case correlated the electrocardiographic changes with serum potassium determinations (which were low), many cases have been reported in which were recorded the electrocardiographic changes in patients with hypopotassemia from various causes. One of the more recent comprehensive reports is that of Bellet and associates,[27] who described the electrocardiographic patterns in a series of seventy-nine patients with hypopotassemia. The commonest findings were low amplitude or inverted T waves, prolongation of the Q-T interval, and prominent U waves. McAllen[28] has challenged the presence of a prolonged Q-T interval in patients with a low serum potassium; in his opinion U waves deform the T waves so that the Q-T interval appears prolonged.

In spite of the many clinical observations little experimental work has been reported on the electrocardiographic effects produced by a deficiency of potassium either in the experimental animal[29,30] or in the perfusate of an isolated heart.[1]

In this study, delayed intraventricular conduction was quite marked in the turtle heart, but there was no or only slight increase in the duration of the QRS interval before the onset of atrioventricular dissociation in the dog heart. The changes in the electrocardiogram of the dog heart were consistent with the changes found in the electrocardiograms of human beings with hypopotassemia.

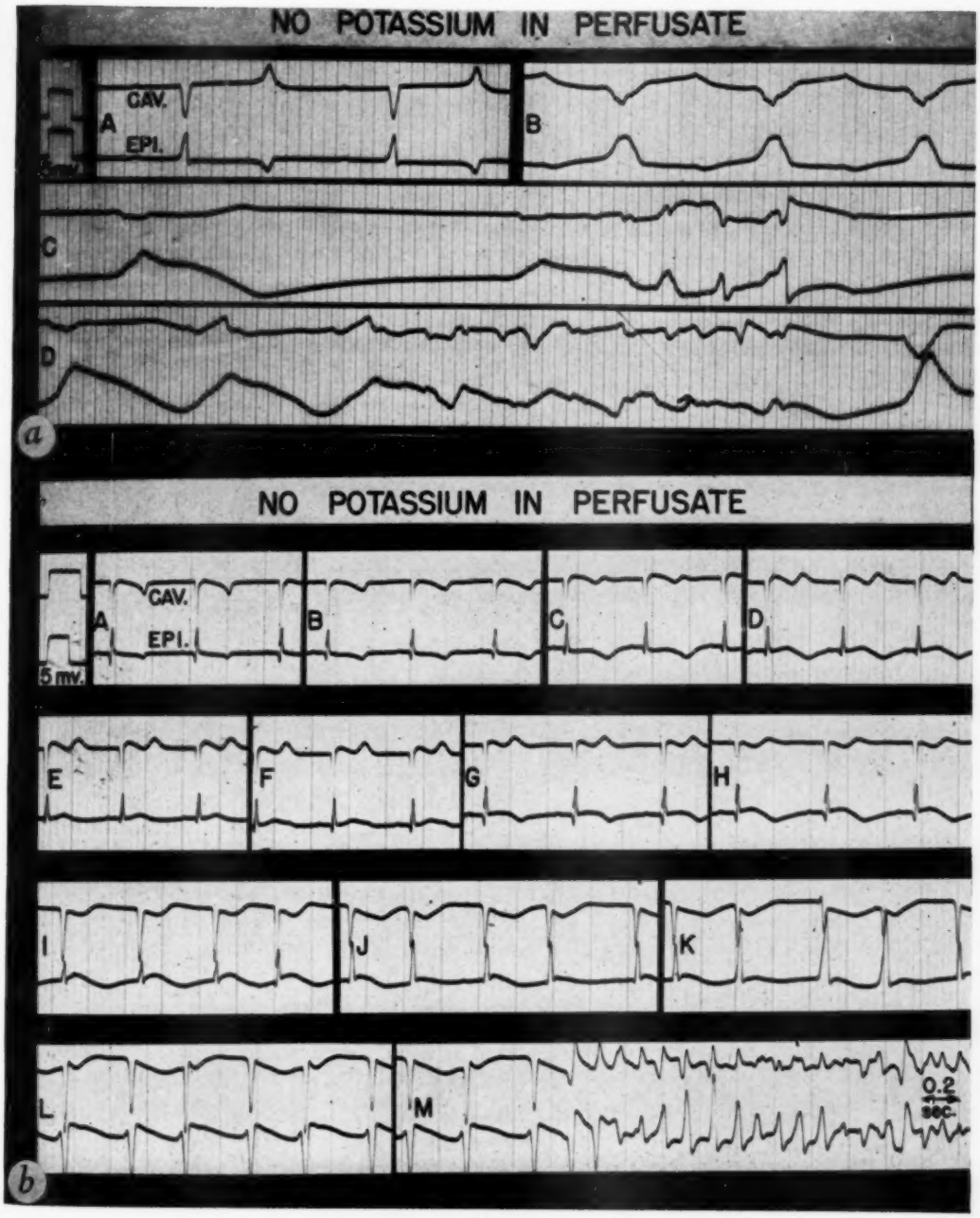
POTASSIUM CONTENT OF HEART MUSCLE AFTER CHANGING CONCENTRATION OF POTASSIUM IN PERFUSATE

In an attempt to gain some knowledge concerning the changes in the concentration of potassium within the heart muscle during the periods of prolonged perfusion with the standard solution (five hours), and after the heart had been subjected to a perfusate containing an excess of potassium or no potassium at all, specimens of the ventricular muscle of the heart of the turtle were analyzed for potassium content.

Duplicate specimens were frozen immediately, crushed, weighed, dried, reweighed, dissolved in 4N hydrochloric acid, diluted with triple distilled water, and analyzed with the flame photometer. The results were expressed as milliequivalents of potassium per kilogram of tissue (Table I).*

*These determinations were made possible by the combined efforts of personnel in the laboratories of Drs. J. L. Bollman, E. V. Flock, and M. H. Power.

a.



b.

Fig. 5.—*a*, Turtle heart. Electrocardiographic changes produced by perfusing a heart with a potassium-free solution. *CAV.*, Electrocardiogram from electrode in ventricular cavity; *EPI.*, electrocardiogram from electrode on the epicardial surface of the ventricle. *A*, Control. *B*, After fifteen minutes of perfusion with a potassium-free solution. *C*, After thirty minutes. *D*, After sixty minutes.

b, Dog heart. Electrocardiographic changes produced by perfusing an isolated heart with a potassium-free Tyrode solution. *A*, Control. *B*, After three seconds of perfusion with a potassium-free solution. *C*, After twelve seconds. *D*, After thirty seconds. *E*, After forty-eight seconds. *F*, After one minute. *G*, After two minutes. *H*, After two and one-half minutes. *I*, After three minutes. *J*, After five minutes. *K*, After six minutes. *L*, After six and one-half minutes. *M*, After seven minutes.

TABLE I. EFFECT OF CHANGE OF CONCENTRATION OF POTASSIUM IN PERFUSATE ON POTASSIUM CONTENT OF HEART MUSCLE

	EXPERIMENT	WATER (PER CENT)	POTASSIUM (MEQ. PER KG. TISSUE)
A. Perfusion with standard solution for one-half hour (duplicate samples)	I A	83.7	61.6
	I B	83.1	65.5
	II A	84.3	61.2
	II B	84.2	63.0
	III A	82.7	65.5
	III B	82.5	65.9
	IV A	83.5	62.7
	IV B	83.3	66.0
	Average	83.4	63.19
B. Perfusion with standard solution for five hours	I A	82.9	68.0
	I B	82.7	70.5
	II A	81.6	72.4
	II B	81.9	71.1
	III A	81.6	75.8
	Average	82.14	71.56
C. Perfusion with potassium-free solution for one hour	I A	82.2	60.9
	I B	81.8	61.1
	II A	80.6	65.4
	II B	80.4	68.9
	III A	83.3	61.3
	III B	82.9	64.3
	IV A	82.6	56.7
	IV B	82.6	57.5
	Average	82.05	62.0
D. Perfusion with excess of potassium (9.81 meq. per liter) in the perfusate until the changes of potassium intoxication had developed	I A	84.9	67.5
	I B	84.1	66.0
	II A	84.0	65.6
	II B	83.5	65.6
	III A	85.1	66.8
	III B	85.0	65.2
	Average	84.4	66.11

Comment.—Prolonged perfusion of the isolated turtle heart with the standard solution increased slightly the concentration of potassium in the tissue with little change in the percentage of water in the tissue. Perfusion of the heart of the turtle with either an excess of potassium in the perfusate (for ten to fifteen minutes) or a potassium-free perfusate (for one hour) resulted in little or no change

in concentration of tissue potassium. If the cells had maintained a constant ratio of intracellular to extracellular potassium, the concentration of total tissue potassium would have greatly increased after perfusion with the solution containing an excess of potassium and definitely decreased after perfusion with the potassium-free solution.

SUMMARY

Action potentials were recorded simultaneously from the cavity and the epicardium of the ventricle of the isolated perfused hearts of the dog and the turtle before and after alteration of the concentrations of the various cations in the perfusate.

The major effects of an excess of potassium on the turtle heart were similar to those on the heart of the dog (prolonged QRS interval, shortened S-T interval, broad P waves, and terminally monophasic or diphasic complexes). However, in the turtle heart the atria and sinus venosus were more tolerant than the ventricle to an excess of potassium; both mechanical contraction and electrical activity of the atria persisted after complete ventricular arrest, while in the dog both mechanical and electrical activity of the atria ceased long before that of the ventricles. An increase in the amplitude of the T wave was observed in the dog and turtle hearts under the influence of an excess of potassium; the width of the T wave was increased or remained the same.

The addition of extra calcium to a perfusate containing an excess of potassium lessened the delay in intraventricular conduction and further shortened the S-T interval produced by the excess of potassium.

Restoration of a low sodium concentration to normal partially reversed the alterations in the electrocardiogram characteristic of an excess of potassium.

In the turtle heart a reduction of the sodium concentration in the presence of an excess of potassium enhanced the effects of the latter. Increase of the sodium concentration in the presence of an excess of potassium partially antagonized the effects of the latter.

Complete absence of potassium from the perfusate prolonged the P-R interval, prolonged the QRS interval, prolonged the S-T interval, and widened the T waves in the turtle heart. Except for slight or no widening of the QRS complex before atrioventricular dissociation developed, similar changes took place in the dog heart when the perfusate contained no potassium. The electrocardiographic changes in the dog heart were consistent with those found in cases of human beings with hypopotassemia.

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A RELATIONSHIP BETWEEN ELECTROCARDIOGRAPHIC CHANGES AND HYPOKALEMIA IN INSULIN-INDUCED HYPOGLYCEMIA

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THE FACTS that serum potassium is lowered by the administration of insulin and that a lowered serum potassium produces changes in the electrocardiogram have been recognized for some time.[1-3] In spite of these observations the changes in the electrocardiogram associated with insulin-induced hypoglycemia have been ascribed to the direct cardiac action of epinephrine, low blood sugar, and to changes in coronary blood flow.[4] The purpose of this study is to point out the relation of serum potassium alterations to the electrocardiographic changes in man in insulin-induced hypoglycemia.

METHOD

Fourteen nondiabetic patients without coronary insufficiency were studied before, during, and after insulin-induced hypoglycemia. In each instance the patient was fasted overnight and, after a control electrocardiogram, blood sugar, serum potassium, and blood pressure were obtained, regular insulin (40 to 80 units) was given intravenously. In three-fourths to one hour, when hypoglycemic symptoms had developed, the determinations mentioned above were repeated and then followed every five to fifteen minutes for the remainder of the study until hypoglycemia was terminated by the administration of glucose. In four of these patients a 10 per cent KCl solution (1.5 to 5 meq.) was given intravenously over a period of one to two minutes at the time when changes in the electrocardiogram were noted. In three different patients 0.5 c.c. (12.5 mg.) Priscoline was given intravenously when the electrocardiographic changes occurred. After the administration of both drugs the electrocardiograms, serum potassium, and blood sugar levels were again determined.

Another group of four patients was given an infusion of epinephrine at the rate of approximately 1 mμ/kg. of body weight per minute and serial electrocardiograms, serum potassium, and blood sugar were obtained. When electrocardiographic changes occurred, the infusion was stopped and after thirty minutes again started; in addition to the epinephrine, 0.5 c.c. (12.5 mg.) Priscoline was given intravenously and the above studies were repeated.

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Serum potassium was determined by the cobaltinitrate method of Looney and Dyer[5] and blood sugar by the Folin-Wu method. In taking the electrocardiogram the standard limb leads and unipolar limb leads were used.

Changes in the Q-T interval were estimated by determining the difference between the measured Q-T interval and that calculated from Bazett's formula[6]: $s = K\sqrt{c}$ where s = Q-T interval, c = cycle length, K = a constant of 0.37 for women and 0.40 for men. If this difference was greater than 20 per cent of the calculated Q-T interval, then the measured Q-T interval was considered prolonged.

RESULTS

The results are shown in Table I. Of the fourteen patients in whom hypoglycemia was induced, all but one (L.T.) showed electrocardiographic changes and a fall in serum potassium. The electrocardiographic changes observed were flattening of the T waves (thirteen patients), S-T segment depression (one patient), and prolongation of the Q-T interval (eight patients). The average fall in serum potassium was 1.89 meq./L. from the control level. All patients with one exception (R.S.) showed a fall in blood sugar below 35 mg./100 c.c. with an average fall of 48 mg./100 c.c. from the control fasting level.

Three of the four patients receiving KCl had reversion of the T wave toward that of the control tracing (Fig. 1). In one the Q-T interval became shorter; in one it did not change; and in two it became longer.

All three of the patients who received Priscoline during insulin hypoglycemia showed reversion of the T waves toward that of the control tracing. The Q-T interval became shorter in one but remained prolonged in the other two (Fig. 1). The serum potassium rose in all to a level close to that of the control pre-insulin potassium value. The blood sugar did not change in two but rose in one.

Epinephrine produced lowering of the amplitude of the T wave in three and prolongation of the Q-T interval in two patients (Fig. 1). There was also a fall in serum potassium and a rise in blood sugar. In one patient there was no change in the electrocardiogram or the serum potassium although the blood sugar did rise.

When Priscoline was given together with epinephrine, two of the patients (M.W. and J.T.) showed no change in the electrocardiogram. In M.W. the serum potassium remained the same as during the control period. In J.T. there was a fall in serum potassium but not as low as during the period of epinephrine infusion alone (Table I). Patient L.M. showed a fall in serum potassium and electrocardiographic changes with lowering of the T-wave amplitude and prolongation of the Q-T interval both with and without Priscoline.

DISCUSSION

It is apparent that the electrocardiographic changes observed in insulin-induced hypoglycemia cannot be attributed to a lowered blood sugar alone since these changes were reversed despite the persistence of hypoglycemia. This is

TABLE I.

EFFECT OF INSULIN

PATIENT	CONTROL		POST INSULIN				POST KCL				POST PRISCOLINE			
	BS (MG./100C.C)	K (MEQ./L.)	BS (MG./100C.C.)	K (MEQ./L.)	ECG T*	ECG Q-T†	BS (MG./100C.C.	K (MEQ./L.)	ECG T	ECG Q-T	BS (MG./100C.C)	K (MEQ./L.)	ECG T	ECG Q-T
R.J.	63	6.5	16	1.2	↓	+								
E.D.	60	4.25	10	3.0	↓	−								
G.B.	57	3.6	15	2.85	↓	+								
A.M.	76	5.3	23	2.68	↓	−								
C.W.	83	5.3	17	1.38	↓	+								
L.T.	69	4.4	32	4.3	O	−								
T.G.	84	5.0	31	3.1	↓	−								
D.W.	64	4.25	10	3.25	↓	−	9	4.25	↑	−				
J.M.	67	4.95	33	2.45	↓	+	30	4.5	↑	+				
G.M.	89	4.4	32	1.9	↓	+	30	....	↑	+				
H.G.	88	2.4	27	1.7	↓	+	15	9.4	O	−				
C.S.	64	5.1	21	2.2	↓	−					14	4.7	↑	+
R.S.	110	3.6	64	3.0	↓	+					80	5.0	↑	−
V.C.	58	3.4	32	1.8	↓	+					28	4.0	↑	+

EFFECT OF EPINEPHRINE

PATIENT	CONTROL		POST EPINEPHRINE				EPINEPHRINE AND PRISCOLINE			
	BS (MG./100C.C.)	K (MEQ./L.)	BS (MG./100C.C)	K (MEQ./L.)	ECG T	ECG Q-T	BS (MG./100C.C)	K (MEQ./L.)	ECG T	ECG Q-T
M.W.	133	3.25	210	1.6	↓	−	111	3.3	↑	−
J.B.	90	2.48	166	2.2	O	−	100	2.2	O	−
L.M.	59	2.4	64	1.7	↓	+	80	1.8	↓	+
J.T.	68	4.8	86	2.0	↓	+	64	3.5	↑	−

*T waves
↓ Decrease in amplitude.
0 No change.
↑ Return of T wave toward the control.

†Q-T interval
+Prolongation of the Q-T interval over the calculated Q-T.
−Normal Q-T interval.

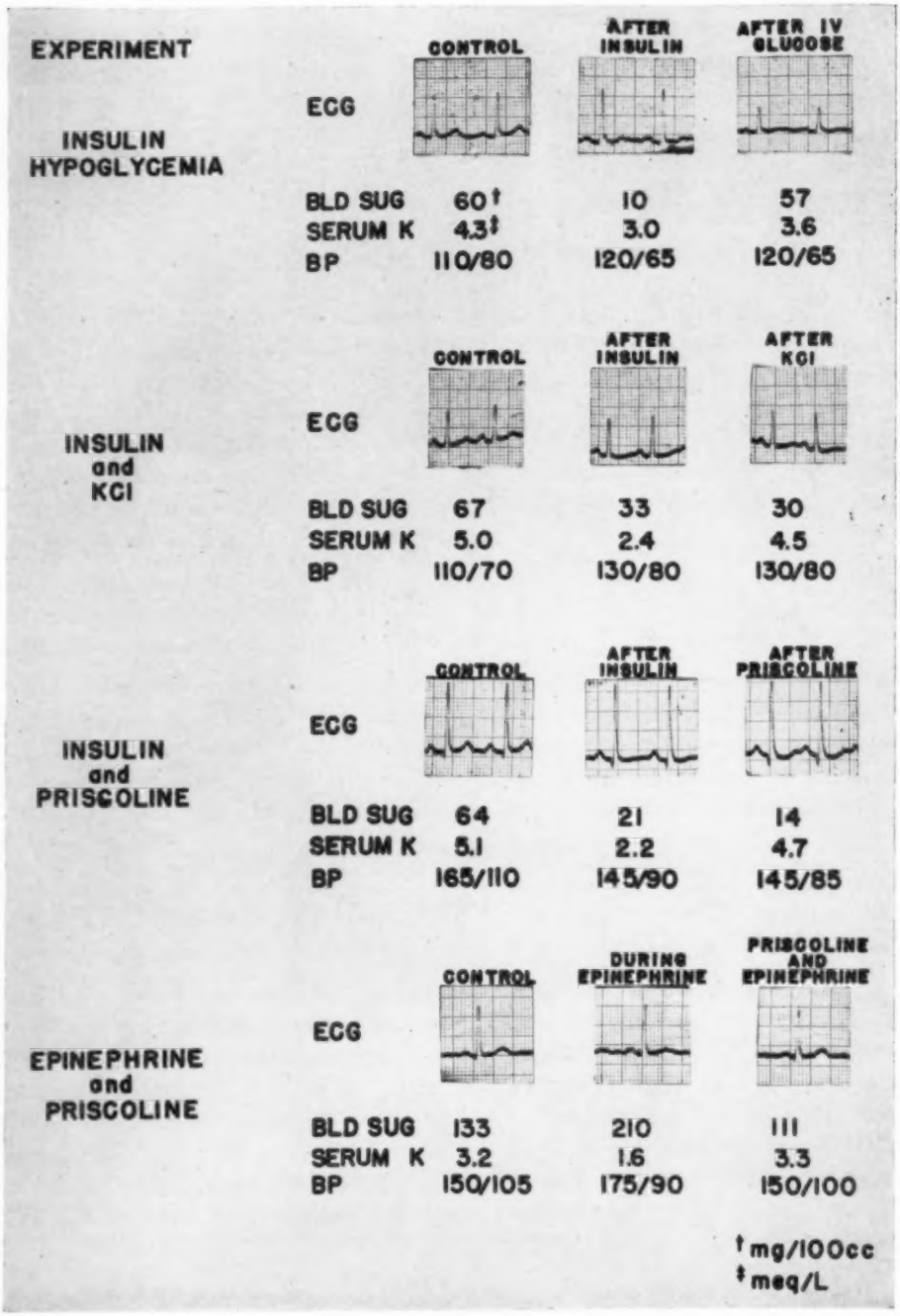
EXPERIMENT
CONTROL
AFTER INSULIN
AFTER IV GLUCOSE
ECG
INSULIN HYPOGLYCEMIA
BLD SUG 60† 10 57
SERUM K 4.3‡ 3.0 3.6
BP 110/80 120/65 120/65
CONTROL
AFTER INSULIN
AFTER KCl
ECG
INSULIN and KCl
BLD SUG 67 33 30
SERUM K 5.0 2.4 4.5
BP 110/70 130/80 130/80
CONTROL
AFTER INSULIN
AFTER PRISCOLINE
ECG
INSULIN and PRISCOLINE
BLD SUG 64 21 14
SERUM K 5.1 2.2 4.7
BP 165/110 145/90 145/85
CONTROL
DURING EPINEPHRINE
PRISCOLINE AND EPINEPHRINE
ECG
EPINEPHRINE and PRISCOLINE
BLD SUG 133 210 111
SERUM K 3.2 1.6 3.3
BP 150/105 175/90 150/100
† mg/100cc
‡ meq/L

Fig. 1.

not surprising since it has been demonstrated that the myocardium does not require glucose as a source of energy.[7,8] On the other hand, it is recognized that serum potassium decreases with the administration of insulin due to a transfer of potassium intracellularly.[3] Hypokalemia from other causes produces electrocardiographic changes with a decreased amplitude of the T wave or its inversion and a prolongation of the Q-T interval.[8,9] These are the changes observed in hypoglycemia.[11] The fact that in all of the patients studied, a fall in serum potassium was associated with electrocardiographic changes resembling those of hypokalemia suggests that these changes are most likely due to shifts in potassium ion. This is in agreement with the findings of Kraft and associates.[12]

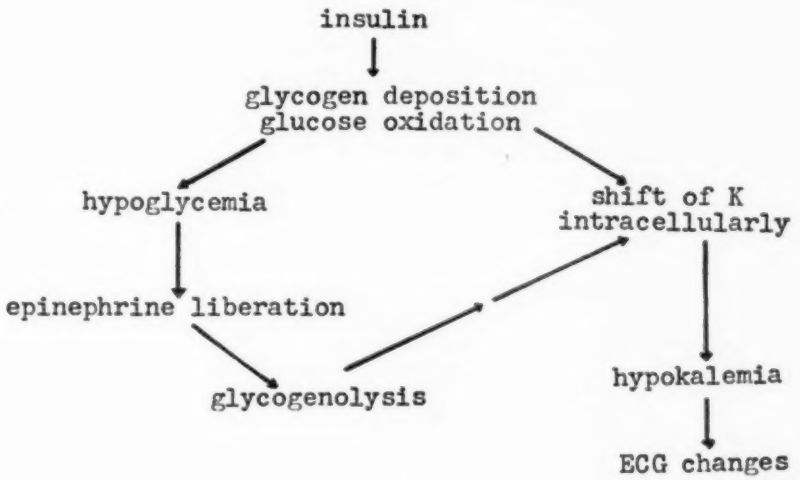

Fig. 2.

The fact that epinephrine injected into man produces a transient rise in serum potassium followed by a prolonged depression in serum potassium,[13] together with the fact that epinephrine-like substances are increased in the blood during insulin hypoglycemia,[15] led us to attempt to block epinephrine action with Priscoline. The reversal of the electrocardiographic changes and rise in serum potassium suggest that such an epinephrine-blocking action might be present and that epinephrine may be the primary agent responsible for the changes in serum potassium observed. This is further supported by the prevention of electrocardiographic and serum potassium changes by Priscoline following epinephrine. Dury[15] thinks that epinephrine is the responsible agent for the fall in serum potassium following insulin administration, but other workers[4] using in vitro studies find that insulin produces a fall in potassium in the absence of epinephrine.

From our results it would seem that in insulin-induced hypoglycemia there are at least two factors which will depress serum potassium. These are insulin[1-3] and epinephrine.[14] It is impossible to say which of these or if it is both that produce the changes seen in hypoglycemia.

It might be postulated that the mechanism shown in Fig. 2 may be operating.

The possibility remains that Priscoline acts by another mechanism to cause potassium to move out of the cells. Electrolyte equilibrium is altered by the shift of potassium and energy expenditure is required to maintain this altered equilibrium. Holland and Greig[16] demonstrated that cholinesterase activity is necessary to preserve the integrity of the erythrocyte and that its inhibition increases the permeability of the cell membrane to sodium and potassium. Priscoline might act by inhibiting cholinesterase.

SUMMARY

1. Fourteen nondiabetic patients were studied before and during insulin-induced hypoglycemia.

2. Changes in the electrocardiograms consisting of decreased amplitude of the T wave and prolongation of the Q-T interval were found to parallel a fall in serum potassium whether this followed insulin or epinephrine injection.

3. It is postulated that the changes in the electrocardiograms seen in hypoglycemia are due to shifts in potassium ion secondary to the effect of insulin and epinephrine on carbohydrate metabolism.

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A CASE OF SPONTANEOUS THROMBOSIS OF THE SUPERIOR VENA CAVA WITH SOME OBSERVATIONS ON THE MECHANISM OF EDEMA FORMATION

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THE SYNDROME of localized congestion and edema consequent to a superior vena cava obstruction is well known. It has been tacitly assumed that the edema in this syndrome results solely from the local increase in venous and capillary hydrostatic pressures. However, recent work has shown that edema associated with venous congestion is accompanied by alterations in renal function. For example, work on the dog suggests that peripheral venous pressure elevation, following constriction of major veins, leads to an increase in renal tubular sodium reabsorption which tends to parallel the extent of venous congestion. As venous congestion declines, through the development of collateral channels, renal sodium excretion returns to normal.[1]

A case of spontaneous superior vena cava obstruction recently came under our care. Studying this case enabled us to make some observations on the genesis of edema in this condition, and to test the response to an oral salt load. The studies suggested that a disturbance in renal function occurred in this syndrome which could contribute to the edema formation.

CASE REPORT

D. S., a 50-year-old white man, was admitted to Michael Reese Hospital on March 12, 1951, complaining of sudden onset of exertional dyspnea, chest pain and cough. Approximately four months prior to admission, the patient developed a chronic nonproductive cough. Two weeks before admission, a fever of 101.5°F. appeared and was successfully treated with penicillin. Four days before admission severe dyspnea on his climbing stairs was noted. This was accompanied by "tightness" and a dull aching pain across the chest. This pain persisted and was made worse by lying down or deep inspiration. Simultaneously, the cough became more frequent, and productive of about one-fourth cup daily of thick white sputum. The dyspnea persisted and edema of the upper body gradually appeared. No fever was noted.

"Inflammatory rheumatism" had been present (approximately eight bouts) between the ages of 15 and 18 years. These were characterized by fever and hot swollen joints. Regression was complete. Recurrence of swollen ankles and joint pains plus stiffness were noted eight months prior to the present admission for which the patient was hospitalized. On the basis of the total picture a diagnosis of low-grade rheumatoid arthritis was made. Treatment consisted of physiotherapy and cortisone injections and led to an uneventful recovery. The family history was noncontributory.

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On physical examination at this admission, the temperature was 100.2° F., pulse 100, respirations 20, and blood pressure in both arms 128/70 mm. Hg. The patient appeared apprehensive and in moderate respiratory distress. The skin of the head, neck, and torso was suffused and of a dusky cyanotic color. In this area there was considerable pitting edema. Dilated veins were visible over the anterior chest wall, the neck, and the head. Venous drainage in this area was downward toward the abdomen. The congestion was symmetrically bilateral and sharply demarcated at the lower level of the rib cage. The remainder of the physical examination was essentially negative except for moderate clubbing of the digits which had been noted in the first admission. Examination of the chest was negative. The lower half of the body was normal.

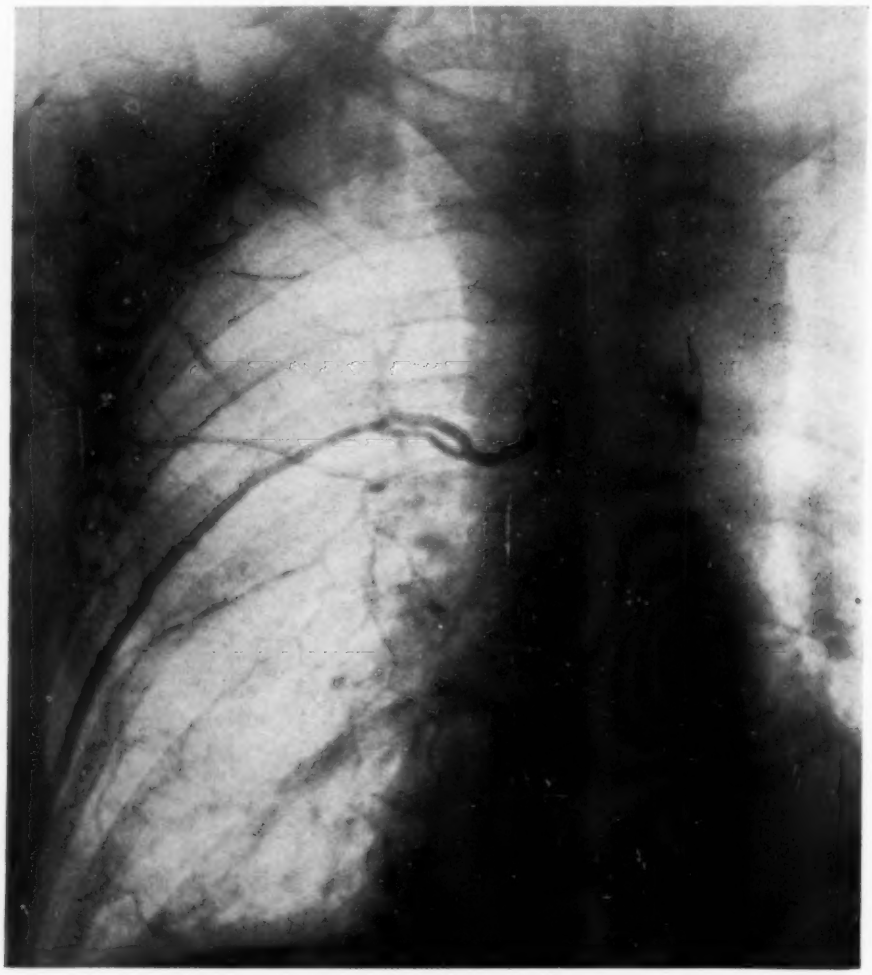

Fig. 1.—Angiocardiogram demonstrating complete occlusion of the superior vena cava with patent azygos vein.

A diagnosis of acute obstruction of the superior vena cava, cause undetermined, was made. An electrocardiogram was read as a borderline curve. Several chest x-ray pictures taken shortly before admission were read as negative. Fluoroscopic examination of the chest on admission showed a widening of the superior mediastinum to the right. A triangular shadow was seen projecting upward and outward from just above the right hilum with rather sharply defined borders. No encroachment upon the lumen of the trachea was noted. The esophagus took its normal course through this area. The lung fields were otherwise clear. A chest film taken three days later showed some fluid in both costophrenic angles but was otherwise unchanged.

The patient continued clinically unchanged for five days. He ran a continuous low-grade fever which never rose above 100.6° F. On the fifth day the temperature became normal and remained normal for the rest of the hospital stay. On the fourth day the patient's cough became "looser" and more productive. Fluoroscopic examination prior to angiocardiography showed fluid at both costophrenic angles plus a linear infiltration in the left lower lung field. There was some dullness to percussion in the left posterior lower chest and occasional rhonchi were heard.

Angiocardiography on the fourth day showed a complete obstruction of the superior vena cava above the entrance of the azygos vein (Fig. 1). Venous pressure in the upper extremities was 440 mm. of saline and a Decholin circulation time was 30 seconds.

The patient was treated with Tromexan which was continued through the course of the hospital stay. Antibiotics were given until April 5. Laminography of the superior mediastinum did not disclose any mass other than the dilated superior vena cava above the obstruction. Examination by an otolaryngologist was negative. The infiltration in the lung fields gradually cleared as did the fluid in the costophrenic sinuses. Numerous sputum examinations were negative for tumor cells and tuberculosis. The rest of the laboratory examinations were noncontributory.

The patient showed a marked improvement in clinical condition on March 17 coincidently with defervescence. This was progressive during his hospital stay. Loss of edema fluid began a few days later and was both mercurial induced and spontaneous. A low-salt diet was not used because it would have interfered with the experimental program.

At the time of discharge, the patient showed only slight edema of the upper body. He had no complaints. Dyspnea was absent; chronic cough still persisted but was less productive. However, venous pressure in the upper extremities was still 320 mm. of saline, and many dilated veins were present over the upper body. The patient still complained of occasional dull chest pain anteriorly. He was discharged ambulatory to convalescence at home and to date has resumed normal activities and has no complaints. Repeat chest films have remained negative.

RESULTS OF SPECIAL STUDIES

Venous pressures were checked in both upper extremities at weekly intervals. It will be noted that they tended to fall gradually, keeping pace with the clinical improvement of the patient (Table I). At the time of discharge, venous pressure was still considerably elevated, an observation which coincides with previous reports that venous pressure tends to remain at high levels although the patient may appear clinically well.[2]

TABLE I. VENOUS PRESSURE IN UPPER EXTREMITIES DURING HOSPITAL COURSE OF PATIENT WITH SUPERIOR VENA CAVA OBSTRUCTION

DATE	VENOUS PRESSURE (MM. H_2O)
3–16	440
3–23	400
3–30	395
4–6	320

In Table II are noted observations on the patient's weight, NaCl intake, and urinary sodium excretion. It will be noted that as he improved clinically his daily food intake increased and this was reflected in his daily ingestion of sodium. Furthermore, improvement was accompanied by a progressive decline in weight (both mercurial induced and spontaneous), despite the fact that no sodium restriction was attempted. Discrepancies between sodium ingestion and

excretion were caused by frequent and profuse nonfebrile diaphoresis, during which sodium was evidently lost.

Despite the difficulty in quantitating sodium excretion it was decided to test the patient's ability to handle an oral sodium load in comparison with a randomly selected normal patient under the same conditions. Enteric-coated

TABLE II. PARTIAL SODIUM BALANCE DATA ON PATIENT WITH SUPERIOR VENA CAVA OBSTRUCTION

DATE	WEIGHT (LBS.)	NA INTAKE (MEQ.)	URINARY NA EXCRETION (MEQ.)	REMARKS
3–20	143	69.0	47.4	
3–21	144	68.8	65.8	
3–22	144	64.4	62.4	
3–23	143	335.4	162.8	Oral salt tolerance
3–24	145	98.6	252.7	
3–25	143	79.2	121.0	
3–26	141	145.8	205.8	Mercuhydrin 2 c.c. IM.
3–27	140	179.9	122.0	
3–28	140	163.6	109.2	
3–29	138	99.6	90.8	
3–30	137	191.8	119.5	

TABLE III. RESULTS OF ORAL SALT LOADING TEST IN PATIENT WITH SUPERIOR VENA CAVA OBSTRUCTION AS COMPARED WITH NORMAL CONTROL*

SAMPLE	HOURS FROM START	URINE (VOL. C.C.)	URINE (NA MEQ.)	AVERAGE URINE EXCRETION (MEQ. NA/HR.)
D.S. (Patient with superior vena cava obstruction)				
1	5.5	150	25.1	4.56
2	13.0	315	61.9	8.25
3	24.0	310	75.8	6.89
4	28.0	130	31.7	7.92
5	33.5	355	77.8	14.15
6	37.0	235	49.1	14.04
7	43.0	255	61.0	10.17
8	49.5	190	33.1	5.10
W.B. (Random control)				
1	4.25	185	13.83	3.25
2	5.5	220	10.77	8.61
3	7.0	210	16.6	11.06
4	8.5	150	19.25	12.85
5	11.75	400	51.3	15.80
6	15.5	210	45.2	12.08
7	24.75	460	80.0	8.65
8	31.75	326	79.6	11.35
9	37.0	269	44.75	8.53
10	48.0	395	53.85	4.89

*Details of the test are given in the text.

sodium chloride tablets were administered orally, 2 Gm. at each meal and 1 Gm. at each intervening hour for a total of 15 Gm. Spontaneously voided urine specimens were analyzed separately during this period. The data is presented in Table III and Fig. 2.

It will be noted that, as compared to the normal, the rate of sodium excretion in the superior vena cava obstruction patient shows a distinct delay. Both patients were at bed rest with bathroom privileges during the course of the experiment.

DISCUSSION

This case of spontaneous superior vena cava obstruction was evidently thrombotic in origin. It afforded an excellent opportunity for observing the natural history of the condition, since most patients exhibiting this syndrome have expanding tumors as an etiological factor. Consequently, the usual case shows not only a progressive lesion but also an increasing debility due to the primary disease.

The patient exhibited the classic signs and symptoms of the syndrome, among which were marked venous distention and venous pressure elevation in the upper body, an altered pattern of venous drainage from the trunk toward the lower body, and substantial edema in the area of venous congestion. It has been generally assumed that the congested tissues become edematous because the elevated venous pressure leads to a rise in capillary hydrostatic pressure. This is presumed to lead to an increased transudation of fluid from the capillary into the extracellular extravascular fluid compartment until the increase in tissue pressure re-establishes a dynamic equilibrium.[3]

The situation is not quite this simple, however. The extensive edema formation of the superior vena cava syndrome involves an expansion of the total extracellular volume of the body, which in turn implies sodium and water retention by the body. The excess extracellular fluid is not "fixed" in the area of elevated venous pressure as would be implied by formation through simple transudation. When our patient became ambulatory, marked edema of the feet occurred, which increased progressively during the day, and tended to decline at night. At the same time, marked facial edema appeared on awakening and disappeared shortly after the patient left his bed. Thus, the excess extracellular fluid was mobile and tended to distribute itself in accordance with the predominant gravitational and hemodynamic forces. Since this excess fluid was not trapped in the area of venous congestion, it could only be retained in the body through an absolute inability on the part of the kidney to excrete the excess sodium, chloride, and water. This line of reasoning was substantiated when an actual test in this patient showed that, compared with the normal, there was a marked impairment of urinary sodium excretion following an oral sodium chloride load (Fig. 2).

The experimental evidence presented in this paper is not conclusive and only suggests that there is renal retention of sodium in the superior vena cava syndrome. However, there is adequate evidence in the literature that venous con-

gestion of itself can lead to an increased renal tubular reabsorption of sodium. Farber and associates[4] have shown that temporary occlusion of the inferior vena cava below the renal veins in man leads to a decreased urinary sodium excretion. The same result has been found during acute tourniquet occlusion of the lower extremities.[5]

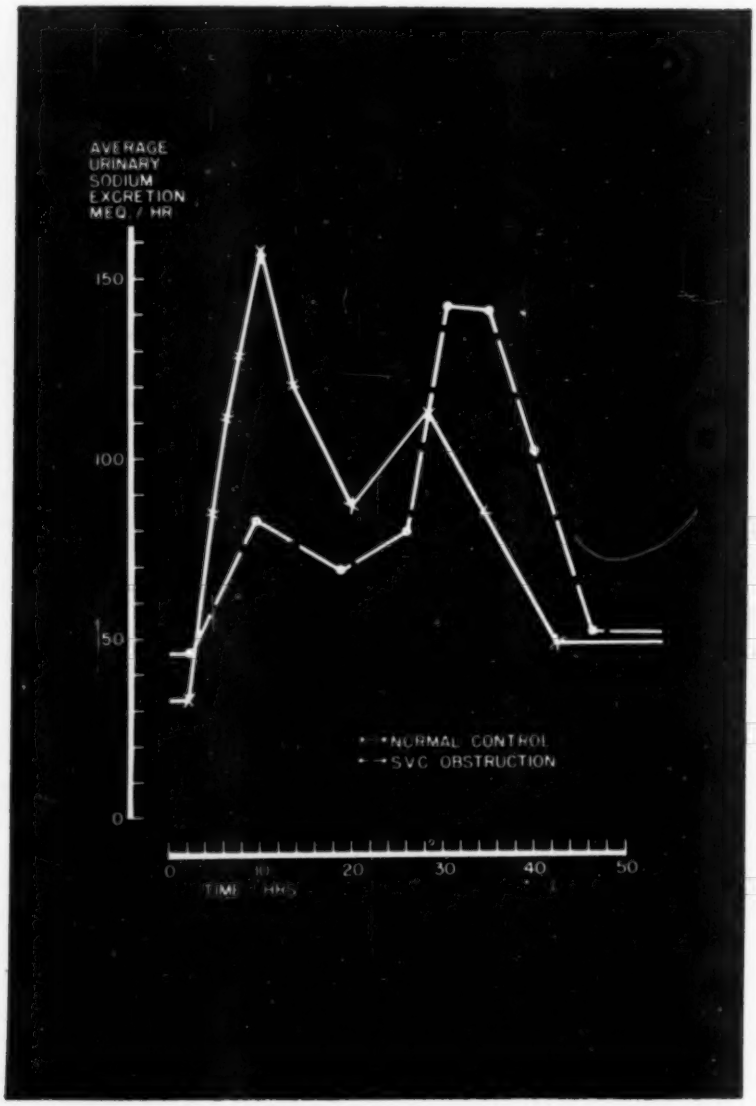

Fig. 2.—Comparison of sodium excretion following oral salt load in normal subject and patient with superior vena cava obstruction. See text.

Investigations on dogs which more closely simulate the superior vena cava syndrome have come from this laboratory. It was shown that chronic hepatic congestion gives rise to increased tubular sodium reabsorption.[6] An extension of this work has demonstrated that chronic congestion in any peripheral venous

bed will lead to an increased renal tubular sodium reabsorption which is independent of any alterations in renal hemodynamics. As the degree of venous congestion declines, renal tubular function returns to normal levels.[1]

The total evidence indicates that an integral part of the superior vena cava syndrome is an alteration in renal tubular physiology in the direction of increased sodium reabsorption.

There are several other aspects to the total problem which may be considered briefly. The mechanism which causes chronic venous engorgement to lead to altered renal tubular function is at present obscure. It seems likely that there is an alteration in the pattern of hormone secretion in the body. The stimulus which initiates and perpetuates this may be chronic circulatory alteration (dehydration reaction?) or an alteration in connective tissue metabolism caused by the circulatory congestion.[1]

In the present study the patient lost edema despite the maintenance of brachial venous pressure elevation of considerable degree. This points to the fact that increased renal tubular sodium reabsorption is not determined by the venous pressure in any particular vein, but by the degree and extent of venous congestion (capillary venous pressure elevation) present. Shortly after the superior vena cava occlusion, both venous pressure and congestion are high in the area of caval drainage. The continuing development of collateral venous channels at the periphery of the obstructed area causes a progressive decline in the area and the degree of congestion. However, the presence of unidirectional valves in the large peripheral veins prevents retrograde flow to areas of lower pressure. Thus, while the total area of venous congestion falls considerably, the major vessels leading into the obstructed superior vena cava continue to show a high venous pressure.

A word may be said about the treatment of patients with superior vena cava obstruction. Very little can be done about the venous obstruction. If due to an expanding lesion, the prognosis is poor; when caused by spontaneous thrombosis, surgical attack upon the thrombus is not necessary. If the patient survives the immediate occlusion, progressive improvement can be expected as collateral circulation develops. Anticoagulants may be given, as in this case, to limit further extension of the thrombus. The edema, always a distressing feature for the patient, can be effectively combated by sodium restriction and mercurials.

SUMMARY AND CONCLUSIONS

1. A case of superior vena cava syndrome apparently due to spontaneous thrombosis is presented.

2. The patient was shown to have an impaired ability to excrete an oral salt load as compared to the normal patient.

3. Evidence is discussed which indicates that the edema formation of the superior vena cava syndrome is due to an abnormal increase in tubular reabsorption of sodium, which parallels the degree of venous congestion.

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A-V CONDUCTION DISTURBANCE IN THE PRESENCE OF THE PRE-EXCITATION SYNDROME

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THE EXPLANATION of the pre-excitation (Wolff-Parkinson-White) syndrome by the presence of an abnormal muscular connection between the auricles and ventricles was based on the observation of a patient with this disturbance in whom normal and abnormal beats succeeded each other. It was observed that, in spite of marked variations of sinus rate, the interval between the normal P waves and the abnormal ventricular complexes was constant showing that these complexes represented conducted beats.[6] The short P-R interval was explained by the absence of a structure similar to the atrioventricular node in this connecting muscle bundle. The atrioventricular node delays the atrioventricular conduction appreciably in an unknown way. The broad QRS complexes were explained by the fact that the excitation reaches the ventricle at an abnormal area and from there spreads abnormally over the heart. The notch before the R wave or in the ascending part of the R wave which is so commonly found in these cases was explained by the initial slow spread of the excitation wave in the common myocardium. As soon as the specific tissue is reached, the spread of the excitation proceeds more rapidly and a tall thin R wave appears.

This explanation has been enthusiastically accepted by White[32] and, when Wolferth and Wood[33] independently arrived at the same interpretation of the abnormality, most cardiologists abandoned other explanations which had been advanced earlier. The final proof for the existence of a muscular connection between auricle and ventricle in the pre-excitation syndrome was apparently obtained when histologic examination of the heart in several cases with the characteristic abnormal electrocardiogram of this syndrome revealed the presence of abnormal connecting muscle bundles.[9,13,28,34]

Further evidence that the pre-excitation syndrome represented a congenital anomaly is its presence in early youth (for instance, in an 8-month-old child)[26] and the fact that it is usually found in individuals who are otherwise perfectly healthy. The discovery of the syndrome in several members of the same family[14] is in favor of an inherited anomaly. It was pointed out[24] that in lower animals the connections between auricle and ventricle are very broad and in man the atrioventricular conduction system is derived from the embryonic auricular canal[11]; the latter represents a broad communication between auricles and ventricles which in ontogenesis is reduced to the small atrioventricular conduction system. Presence of abnormal connecting fibers is, therefore, comprehensible as a congenital anom-

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aly. In many communications the anomalous atrioventricular connection was designated as the bundle of Kent.[6,33] Kent had found such muscular connections under certain conditions and similar connections were seen by others. The fact has been stressed that the term "Kent-bundle syndrome" is purely descriptive and does not exclude the presence of other atrioventricular connections.[21]

Many other explanations offered since 1932 have been critically reviewed elsewhere,[15,31] and will not be discussed here.

Recently, however, reconsideration of the problem has been made necessary by new important facts. Thus, anatomic examination of the hearts from some patients with the pre-excitation syndrome did not disclose the presence of abnormal connecting bundles.[5] In one instance of the pre-excitation syndrome Segers and associates[29] saw the sinus rhythm change to atrioventricular rhythm without visible P waves and without affecting the form of the abnormal, characteristic QRS complexes. One would assume that with the appearance of atrioventricular rhythm normal QRS complexes should be recorded unless the stimulus originates in the abnormal connection itself and excites auricles and ventricles simultaneously. There is no proof that stimuli originate in the anomalous connection. Indeed, in other observations showing change from sinus rhythm to atrioventricular rhythm the abnormal QRS complexes did disappear.[15,16] The assumption of the normal form by the ventricular complex when the pacemaker shifts from the sinus node to lower levels "suggests that anomalous atrioventricular excitation is impossible when ventricular excitation occurs simultaneously with, or precedes auricular."[16]

Other observations which are important in this context concern the appearance of the pre-excitation syndrome in animals and in patients during catheterization of the heart while the tip of the catheter is in contact with the ventricular wall in the area of the septum and pulmonary conus. Such tracings were obtained in the experimental animal [1,3,30] and in two patients.[8] Frau and Maggi[4] were able to produce in dogs tracings with the pre-excitation pattern by mechanical stimulation of the conus of the right ventricle or by injections of Adrenalin into the upper septum. Finally, Segers[27] saw, in one case, normal sinus beats alternate with abnormal beats clearly exhibiting the pre-excitation pattern, but with occasional ventricular extrasystoles showing the same complex as the presumably aberrantly conducted sinus beats. While the objection is possible that we are actually dealing here with extrasystoles in all tracings, that is, with extrasystoles which have a long coupling so that a normal P wave appears a few one-hundredths of a second before the extrasystole by coincidence, another observation reported in the same paper is more difficult to explain. A young woman presented the pre-excitation syndrome intermittently. The electrocardiogram revealed two types of P waves, only one of which was followed by abnormal ventricular complexes after a short P-R interval. The changes in the P waves in connection with this syndrome have been stressed before.[7] Segers also found on the isolated rabbit heart, perfused by the Langendorff method, that injection of a 1 per cent solution of strychnine into the wall of the left ventricle led in a

number of instances to the appearance of premature ventricular contractions, revealing the form typical of the pre-excitation syndrome. In some of these experiments again two different types of P waves appeared, and the abnormal ventricular beats followed only one type of P wave and were absent after the other.

These observations revived the theory that the pre-excitation syndrome is due to an abnormal stimulus formation and not to a disturbance of conduction. This possibility had already been considered and rejected.[6] It was thought possible that the auricular contraction might discharge an irritable focus in the ventricle by means of mechanical stimulation. It was pointed out that under certain experimental conditions, namely, after treatment of the heart with aconitine, the slightest mechanical stimulus, such as gently touching the epicardial surface with the back of a knife, may lead to the rhythmic discharge of rapid stimuli.[18] Consequently, auricular contractions could theoretically elicit stimuli within the ventricles because of sudden stretch during the filling period. In the primitive heart the diastolic filling represents the physiologic stimulus for formation of the heart beat and under certain experimental conditions stretch and pressure cause extrasystoles to appear.[23]

The following observations of two instances of the pre-excitation syndrome seem to us of importance in the present controversy regarding the mechanism of origin of the abnormal ventricular activation. Both concern instances of atrioventricular block.

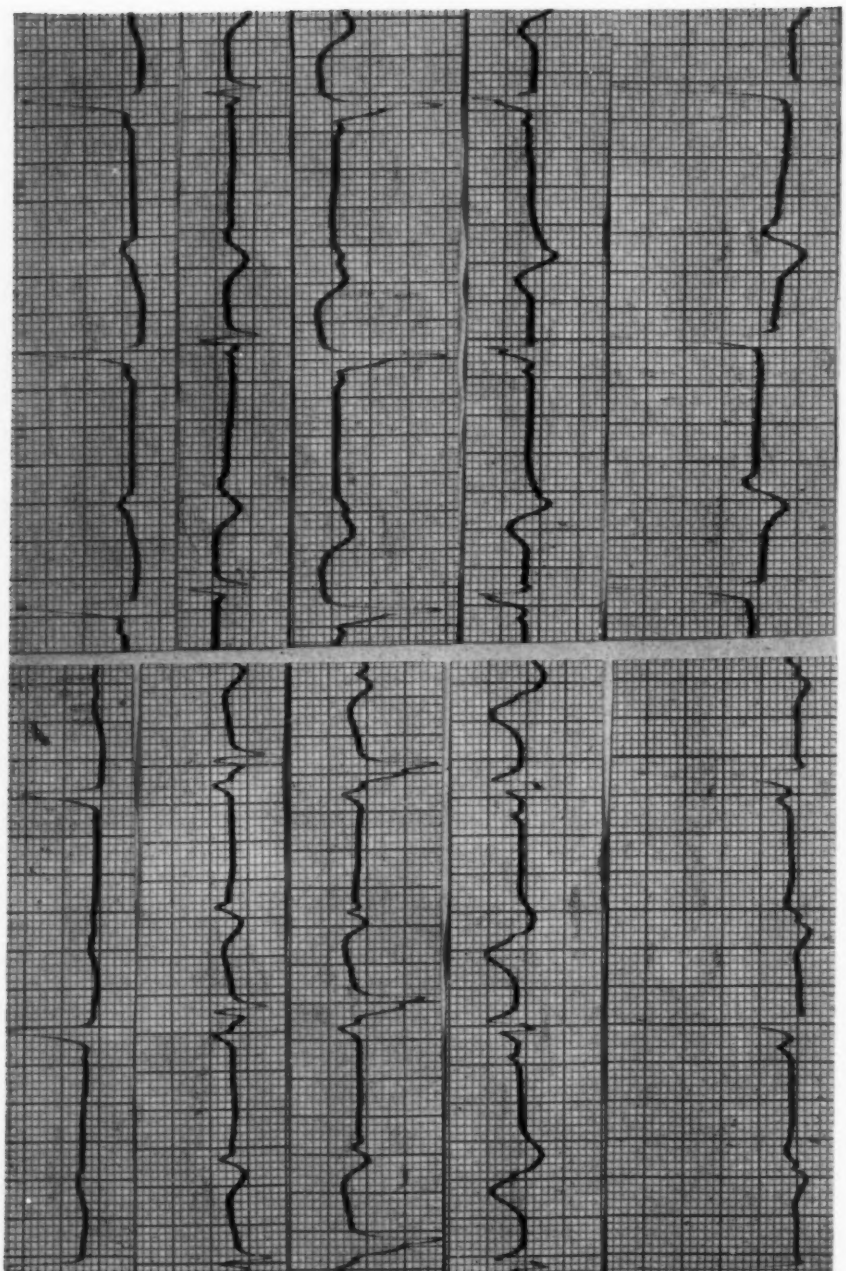
CASE REPORTS

CASE 1.—A 71-year-old woman had a history of hypertension and of a myocardial infarction prior to admission. She was admitted to the Metropolitan Hospital because of severe chest pain and several attacks of unconsciousness. There was no history pointing to attacks of paroxysmal tachycardia. The clinical findings and the electrocardiogram indicated the presence of an acute infarction, located on the posterior wall of the left ventricle.

The electrocardiogram (Fig. 1, *A*) shows a bradycardia of 45 beats per minute and an auricular rate of 90 with a 2:1 block. The conducted beats have a short P-R interval of 0.10 second and the QRS complexes show the common form of the pre-excitation syndrome with the slurring of the ascending limb of the R wave in Leads I and V_5. The pattern of the ventricular complexes is compatible with the diagnosis of an acute posterior wall infarction. This is more pronounced in another tracing obtained three days later (Fig. 1, *B*) which reveals the persistence of a 2:1 block. The tracing shows that the P-R interval of the conducted beats is now shortened in all leads to 0.08 second. The form of the P waves is changed. A prolongation of the Q-T interval persists. One week later, another electrocardiogram (Fig. 2) was obtained. Here we see in every lead a series of conducted beats with a P-R interval of 0.10 second. There is a shortening by 0.01 to 0.02 second of the P-R interval in the first conducted beat after the dropped beat, and a lengthening in the following ones, particularly visible in Leads I, III and V_2. The electrocardiographic pattern of the QRS complexes had changed markedly. The tracing shows changes of the T wave dependent on the duration of the preceding diastole (most distinctly in V_2) which are probably connected with different strength of systole due to greater filling after a longer pause.[19]

One attack of Stokes-Adams syndrome occurred shortly after the patient's admission. The patient recovered fully and was discharged in good condition. Almost daily, electrocardiograms, were taken which showed persistence of the pre-excitation pattern. At no time were normally conducted beats seen.

A report obtained from another hospital to which the patient had been admitted six months before revealed the presence of the pre-excitation syndrome and a 2:1 block with fainting spells even at that time.



A. *B.*

Fig. 1.—*A*, 2:1 A-V block with evidence of a posterolateral wall infarction and the pre-excitation syndrome; *B*, the P-R interval is shorter.

We are, therefore, dealing with a patient with hypertension and coronary sclerosis who had an attack of coronary occlusion with a Stokes-Adams syndrome. The electrocardiogram showed the pre-excitation syndrome with 2:1 block, and later groups of conducted beats with a shortening of the P-R interval after the block and a slight lengthening in the succeeding conductions. Because of this phenomenon and the absence of multiple successive blocked beats, an atrioventricular conduction disturbance of the type of Wenckebach periods must be diagnosed.

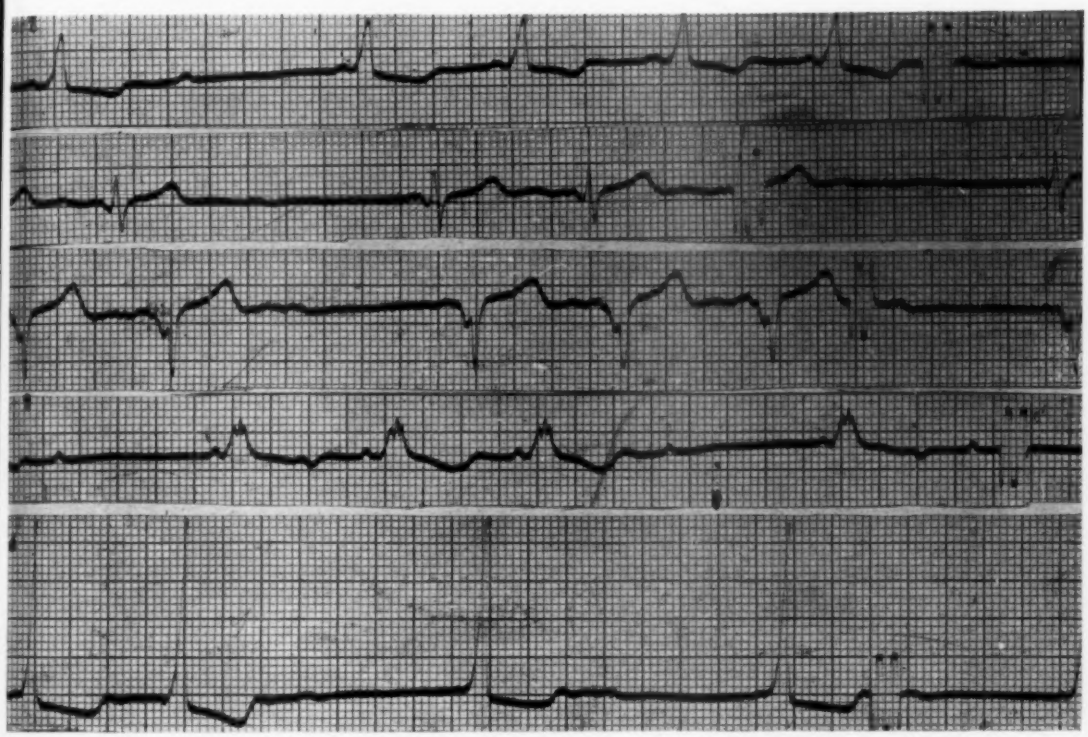


Fig. 2.—Same patient as in Fig. 1. Periodically dropped beat during the presence of a pre-excitation syndrome.

CASE 2.—A 10-year-old girl was admitted because of severe attacks of palpitation. The history revealed only whooping cough several years prior to admission. The attacks of palpitation lasted minutes or hours. In recent months the attacks were more prolonged and evidence of congestive heart failure had developed. For this reason the patient had received digitalis.

An electrocardiogram, obtained shortly after admission, shows in Lead I wide, slurred and notched P waves with a P-R interval of 0.20 second followed by normal QRS complexes and T waves showing effect of digitalis therapy (Fig. 3).

When Lead II was taken the rhythm had changed. The P-R interval measures 0.08 second and the QRS complexes are widened with the characteristic notch of the ascending part of the R wave. Abnormal QRS complexes are present in the other leads. The P waves are peaked and negative in Lead III; the P-R interval persists at 0.08 second throughout the other leads. The diagnosis of an atrioventricular rhythm does not seem justified on the basis of the inverted P waves in Lead III alone; also, this would not explain the changes of the QRS complexes which are rather characteristic for the pre-excitation syndrome.

It was possible to register the electrocardiogram during an attack of tachycardia (Fig. 4*). In each standard lead an auricular tachycardia with a rate of 210 is easily recognized. The P

*This figure has been shown elsewhere[21] and is reproduced here with permission of the publisher.

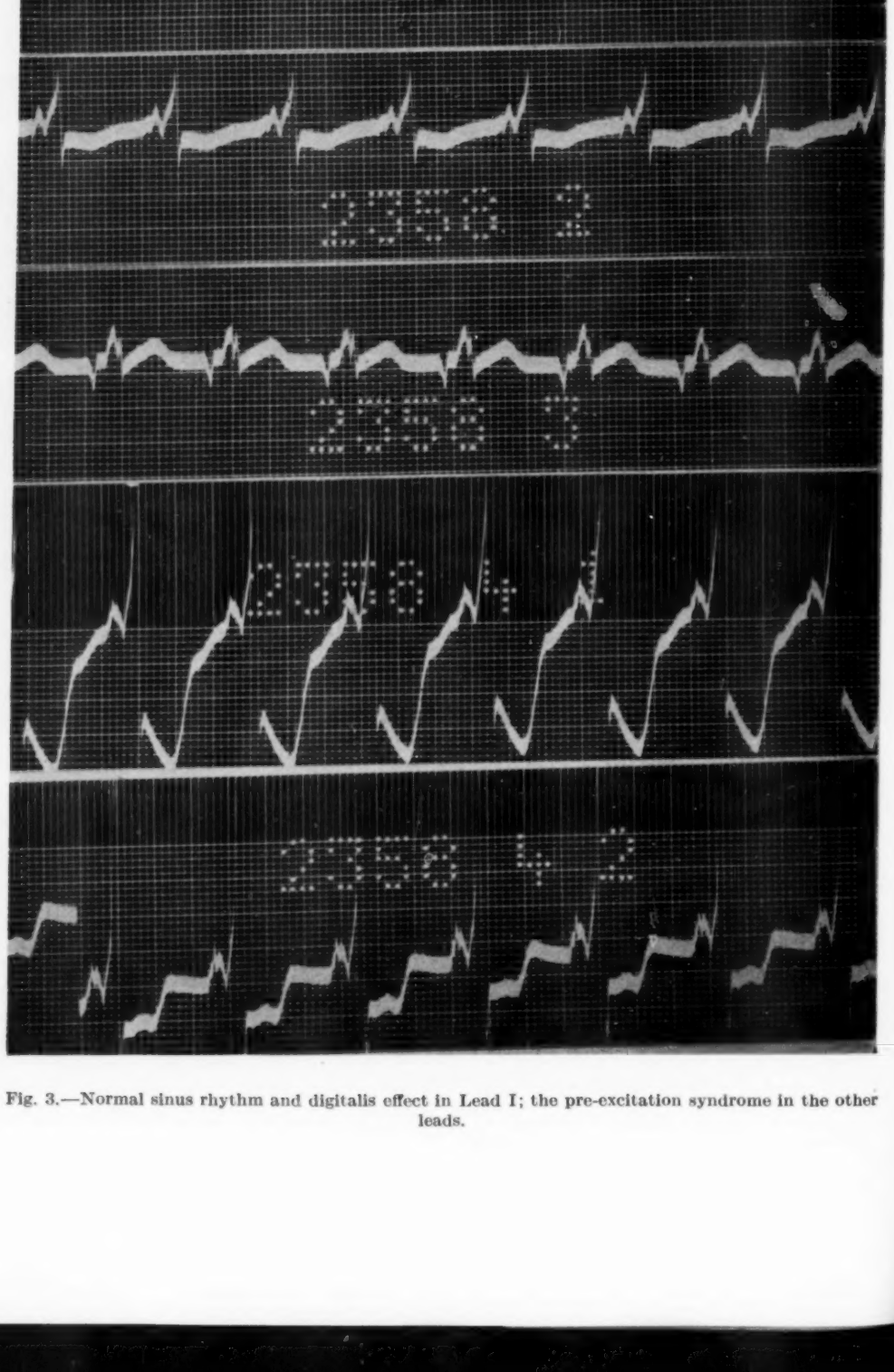


Fig. 3.—Normal sinus rhythm and digitalis effect in Lead I; the pre-excitation syndrome in the other leads.

waves are positive in Leads I and II; they are negative in Lead III. In each lead two types of QRS complexes are seen. There are thin QRS complexes of normal configuration as well as widened and slurred ones. In Lead I inverted T waves are distinctly visible. In Lead I an abnormal QRS complex at the beginning of the tracing follows the P wave after an interval of 0.14 second and the next two QRS complexes with normal form have a P-R interval of 0.24. Then follows a series of abnormal beats conducted with a P-R interval of 0.14 second. In the first part of the tracing of Lead II, only abnormal ventricular complexes are visible. An alternation of 2:1 and 3:2 block exists. The first conducted beat after a block has a P-R interval of 0.08 second. If a second conduction follows, which happens twice, the second beat has a longer P-R interval amounting to 0.10 second. In the last two groups of Lead II the first beat is abnormally conducted and has a short P-R interval while the second has a much longer P-R interval and is followed by a normal QRS complex. A series of such normal beats is seen at the end of the tracing. A 2:1 block and occasionally groups of 3:2 block also appear in Lead III with the long P-R intervals and without widened QRS complexes. Only the penultimate QRS complex in Lead III follows after a P-R interval of 0.08 second and is abnormally widened.

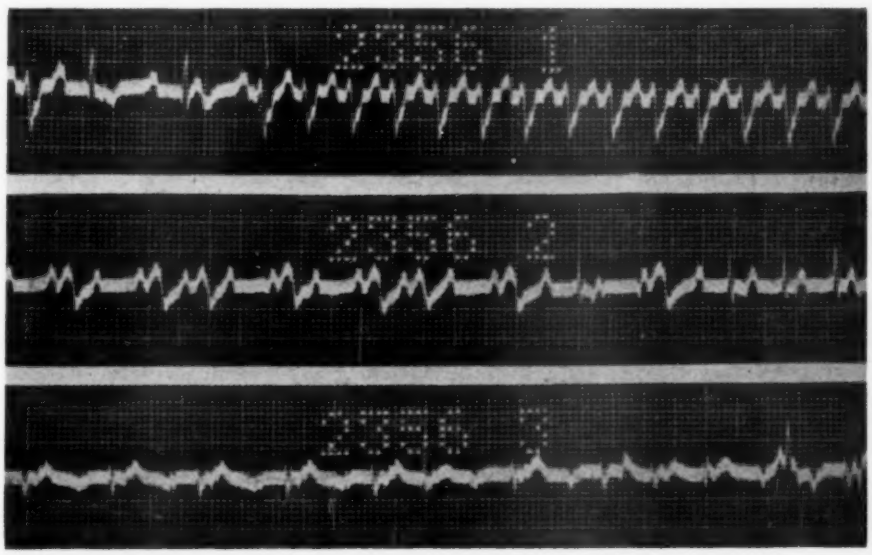


Fig. 4.—Paroxysmal auricular tachycardia; some of the auricular beats are conducted over the atrioventricular system and some use an anomalous path. (Reprinted with the permission of the J. B. Lippincott Company.)

Therefore, we may conclude that this tracing shows the presence of a paroxysmal auricular tachycardia throughout. Some of the auricular beats are conducted over the normal atrioventricular system in the usual way and reach the ventricles with a slight delay, possibly due to the administration of digitalis or because of the high rate. Some of the beats use an abnormal pathway. A paroxysmal auricular tachycardia with abnormal complexes is seen in Lead I and one with normal complexes at the end of Lead II. In all leads different degrees of partial atrioventricular block are seen, namely, prolonged P-R intervals, 2:1 block, and 3:2 block with prolongation of the second P-R interval. Sometimes as in Lead II (on two occasions) and once in Lead III the first stimulus after a block uses the abnormal path while the second one or the following ones are normally conducted.

Of particular importance in this case of pre-excitation syndrome is the presence of gradual prolongation of the P-R interval during abnormal ventricular excitation (see Lead II).

DISCUSSION

Both cases exhibited an atrioventricular conduction disturbance during the presence of the pre-excitation syndrome. In the first case periodically dropped beats and 2:1 block were found during the presence of sinus rhythm, while the second case revealed periodically dropped beats during an attack of paroxysmal auricular tachycardia. In this case the atrioventricular block was seen during the normal atrioventricular conduction as well as during the anomalous conduction.

It seems safe to assume that in the first case the normal atrioventricular conduction system did not function since no normal conduction was observed even during the long pauses. Since the patient had at least one posterior wall infarction and atrioventricular block is not uncommon in this condition a block of the normal atrioventricular conduction is understandable. One cannot help speculating whether in this patient, who suffered from attacks of Stokes-Adams syndrome, the accessory pathway was not a lifesaving structure, permitting auricular stimuli to reach the ventricles when the normal atrioventricular path was interrupted.

If one examines the possibility of explaining the tracings of Case 1 as being caused by a disturbance of stimulus formation and not by a conduction disturbance one must concede that it is theoretically possible for an ectopic center in the ventricle to respond only to every second mechanical stimulus connected with the auricular systole. The 2:1 response to regular rhythmic stimulation is a well-known fact in cardiac physiology. The shortened P-R interval after a dropped beat and the lengthening thereafter speaks against a disturbance of stimulus formation and is, on the other hand, typical for a disturbance of conduction (Wenckebach phenomenon).

In the second case only a disturbance of conduction can be considered. The presence of a distinct Wenckebach phenomenon during the period of anomalous conduction strongly favors, in our opinion, our original explanation of the pre-excitation syndrome, namely, atrioventricular conduction over an anomalous pathway.

Against the explanation of the pre-excitation syndrome by the presence of ectopic centers in the ventricle which are awakened by the auricular contraction is the observation that during auricular fibrillation some stimuli are normally and some abnormally conducted.[24] The abnormally conducted beats have the same form during auricular fibrillation and during the presence of sinus rhythm in the same case, and when abnormal beats are present the same fibrillation arrhythmia prevails as during the fibrillation with normal atrioventricular conduction.

We found in the literature three other observations of block during the presence of the pre-excitation syndrome. Coelho describes a 62-year-old woman with a history which is remarkably like that of our Case 1.[2] The patient had hypertension and attacks of Stokes-Adams following a posterior wall infarction.

Tracings obtained from this patient showed a 2:1 block in the presence of short P-R intervals with the characteristic abnormal QRS complexes. Several conducted beats in succession, as in our case, were not observed. However, when the 2:1 block changed into complete atrioventricular block the QRS complexes of the pre-excitation syndrome disappeared. Contrary to the interpretation of the author this fact speaks, in our opinion, for an anomalous conduction and against extrasystoles from an irritable center.

In another patient[28] the pre-excitation syndrome was observed during an auricular tachycardia with a rate of 135 and 2:1 block. During carotid pressure the P-R interval increased from 0.06 to 0.11 second but the QRS complexes maintained their form. This observation also proves, in our opinion, the presence of an anomalous conduction.

In another 62-year-old woman with a posterior wall infarction, complete atrioventricular block was found but occasionally auricular stimuli were conducted with the characteristic short P-R interval from auricles to ventricles.[9]

Two more observations require discussion. They are the appearance of the pre-excitation syndrome during cardiac catheterization in animals and in man, and the persistence of the syndrome when the rhythm changes from sinus rhythm to atrioventricular rhythm.

There is no doubt that the abnormal beats during catheterization are caused by the mechanical stimulation of the wall of the septum or other areas of the ventricles by the catheter. Mechanical stimulation of the endocardium and subjacent specific fibers has been known for many years to cause heterotopic stimulus formation. An experimental study of heterotopic ventricular beats in the dog revealed that the rate of the ectopic rhythm elicited by mechanical stimuli is similar to that of the existing sinus rhythm in the same animal.[17] Thus, with a rate of the sinus rhythm of 170 that of the ectopic rhythm was 140, with a rate of the sinus rhythm of 130 the rate of the ectopic rhythm was 130. If the sinus rhythm had a rate of 110 the ectopic rhythm had the same rate. Even if in the same experiment the rate of the basic rhythm slowed down, the ectopic rhythms, caused by mechanical stimulation, slowed down in a parallel manner. A similar parallelism was recently shown to exist during parasystole where again the basic rhythm and ectopic rhythm were of almost equal rate.[22] Under these conditions, when an ectopic center sends out stimuli at the same rate as the sinus node, for a short time groups can be observed which resemble the pre-excitation syndrome since the P waves are followed after a shortened distance by an abnormal ventricular complex. Actually the inspection of the tracings, particularly those published by Sodi-Pallares and associates[30] and Biork and Krook[1] shows that the two rhythms are independent because the P-R interval changes and P waves disappear in the QRS complex. We consider therefore the appearance of complexes resembling the pre-excitation syndrome during cardiac catheterization as fortuitous, caused by the similar rate of existing sinus and ectopic rhythms.

The persistence of an abnormal ventricular complex during change from sinus rhythm to atrioventricular rhythm is compatible with the assumption of an anomalous conduction if one recalls that the abnormal pathways need not be present only on the lateral wall of the heart but may exist in the septum. The

investigations by Mahaim and Winston[10] showed abnormal "paraseptal" connections between the upper Tawara node and the septal common cardiac muscle. These connections would explain the persistence of the pre-excitation syndrome during atrioventricular rhythm while it would disappear if the connecting muscle bundles were present on the lateral wall of the heart.

The persistence in Fig. 4 of an auricular paroxysmal tachycardia with the auricular stimuli being conducted normally for a time over the atrioventricular system and then abnormally for a short while argues against the explanation of the tachycardia by a circus movement between auricles and ventricles.[12] Reversed conduction in the auricle should reveal the characteristic low P waves in Lead I and deeply negative, peaked P waves in Leads II and III. Actually, the mechanism of the paroxysmal tachycardias, including paroxysmal fibrillation in seventy per cent of the patients exhibiting the anomalous conduction, is still not clear. Ventricular tachycardias have also been described but most of the cases we found in the literature showed only anomalous conduction during auricular tachycardia or auricular fibrillation. In our opinion the best explanation for the frequent occurrence of tachycardia is one which assumes that occasionally an auricular stimulus conducted over the normal atrioventricular pathway is immediately conducted back to the auricle over the anomalous path. It is known from an impressive body of experimental work that any stimulus applied to the heart at the end of systole or early diastole (the so-called critical or vulnerable period) may lead to repetitive response and heterotopic stimulus formation.[20,25] If a stimulus originating in the ventricle is reversedly conducted to the auricle and then again reaches the ventricle early in diastole over the anomalous muscular connection a paroxysmal ventricular tachycardia may appear.

We are, however, unable to explain the occurrence of the pre-excitation syndrome only after abnormally formed P waves[7,27] and the occurrence of ventricular extrasystoles of the same form as the anomalously conducted beats.[2,27] These observations cannot be explained by any theory so far offered. Even if one assumes the existence of an irritable center in the ventricle it is hard to believe that this responds only to one and not to another type of conducted stimulus.

SUMMARY AND CONCLUSIONS

The two most important explanations of the pre-excitation syndrome, namely, abnormal atrioventricular conduction and abnormal beats originating in an irritable ectopic focus, are re-evaluated in view of new observations.

Two cases of the syndrome are described which show atrioventricular conduction disturbances in the presence of the pre-excitation syndrome. The opinion is expressed that these observations prove the existence of anomalous conduction in these cases.

An explanation is offered for the frequent occurrence of paroxysmal tachycardias in these cases.

Certain observations, however, still remain inexplicable in terms of an anomalous atrioventricular conduction.

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IDENTIFICATION OF THE COMPLEXES OF THE ELECTROMAGNETIC BALLISTOCARDIOGRAM IN A SINGLE CHANNEL

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WITH the introduction of simplified and compact instruments[1] ballistocardiography has become a practical office procedure. The electromagnetic ballistocardiograph seems to have become more popular than the photoelectric cell type because of several advantages.[2] However, one of the limitations of the office use of this instrument has been the lack of adequate means of certain identification of the ballistocardiographic complexes with the ordinary single-channel electrocardiographic recording instrument. The first attempts at introducing the QRS complex of the electrocardiograph as an identifying agent of the ballistocardiograph in a single channel[3] did not permit selective damping of the electrocardiograph so that distortion of the ballistocardiographic waves frequently occurred. An attempt was then made[4] to damp selectively the superimposed electrocardiograph so that this distortion would be minimal. However, using the circuits previously described, the desired objective could not be achieved with the electromagnetic ballistocardiograph.

The following electrical circuits and arrangements were found to permit selective damping of the superimposed complexes of the electrocardiograph for identification purposes without appreciably altering the electromagnetic ballistocardiographic patterns.

The ballistocardiographic and electrocardiographic circuits should be connected in series and a variable resistance (rheostat) of 0 to 1,000,000 ohms connected in parallel across the electrocardiographic leads (Fig. 1). By adjusting the rheostat, varying resistances of from 0 to 1,000,000 ohms may be obtained. The amplitude of the QRS of the electrocardiograph may then alone be selectively diminished without affecting the amplitude of the regular ballistocardiographic waves (Figs. 2 and 3). As can be seen, the voltage of the QRS marker can be decreased at will to prevent distortion of the ballistocardiogram or indeed be entirely eliminated. Although a rheostat of up to 1,000,000 ohms was used here, in actual practice one that varies from 0 to 100,000 ohms is more practical for the range employed.

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Although the pattern of the normal ballistocardiogram can generally be easily determined, in abnormal cases the waves may be quite bizzare and defy identification. It is obvious that the QRS of the electrocardiogram superimposed on the waves of the ballistocardiogram will permit identification of the latter in obscure cases. It can be seen from the illustrations that in the normal individual the QRS complex of the electrocardiogram always just precedes the "H" wave of

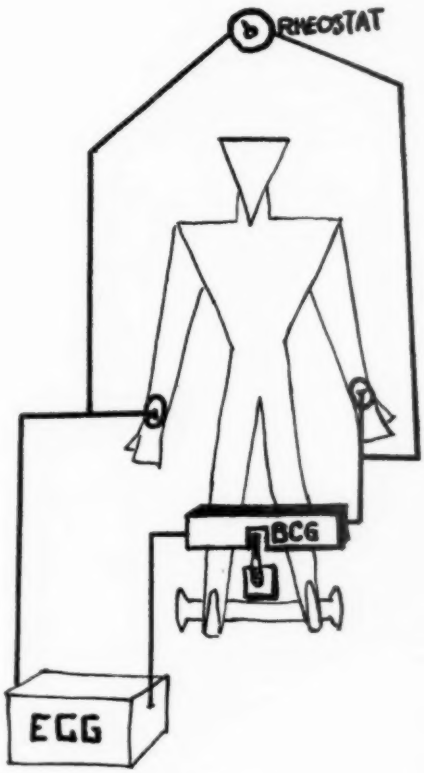

Fig. 1.—Arrangement of the electrical circuits and elements. The electromagnetic ballistocardiograph is connected in series with the electrocardiographic circuit. A variable resistance (rheostat) of 0 to 1,000,000 ohms (preferably 0 to 100,000 ohms) is placed in parallel across the electrocardiograph lead wires being utilized. Selective simultaneous recordings such as seen in Figs. 2 and 3 are then possible.

the ballistocardiogram and thus identifies it. The identification of the "J" peaks in the normal also depend on a time relation after the occurrence of the QRS. The significance of this relation has been the source of some investigation.[5]

SUMMARY

Because of several advantages, the electromagnetic ballistocardiograph has become a practical office instrument. Previously described arrangements of the electrical elements and circuits have not been satisfactory for identification of the complexes derived from this instrument. A new arrangement has been described which will permit simultaneous recordings of the waves of the electromagnetic ballistocardiograph and the electrocardiograph patterns on an ordinary single channel electrocardiographic machine with selective damping of the latter for

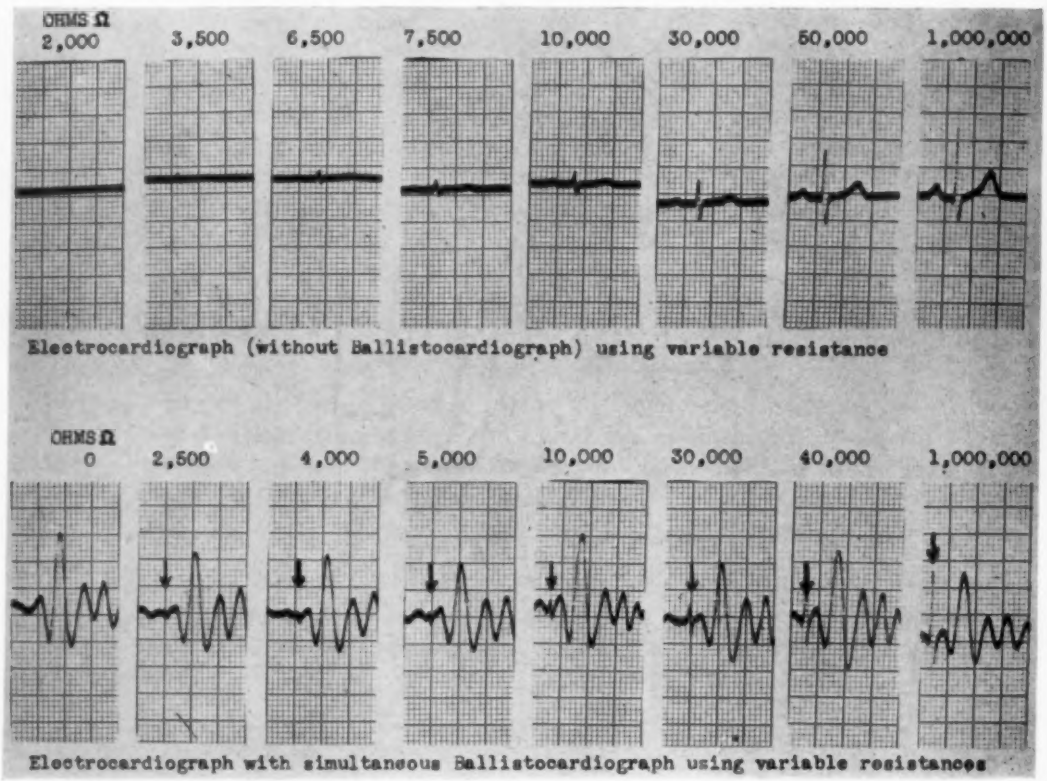

Fig. 2.—The electrocardiogram is recorded at various resistances of the rheostat which controls selectively the amplitude of the QRS complexes. It is obvious that with 0 ohms' resistance the ballistocardiogram completely predominates and the electrocardiogram is not visible. The optimal range of resistances is between 2,500 and 30,000 ohms. In this range the QRS is small but distinctly visible. Above it the QRS is too large and may distort the ballistocardiographic waves.

purposes of identification. The arrangement permits selective damping of the electrocardiographic waves to the point where the QRS is just discernible without affecting the amplitude of the ballistocardiograph or significantly distorting its pattern. The circuits can be applied to either the radio vacuum tube amplifier or the string galvanometer types of standard electrocardiograph recording machines.

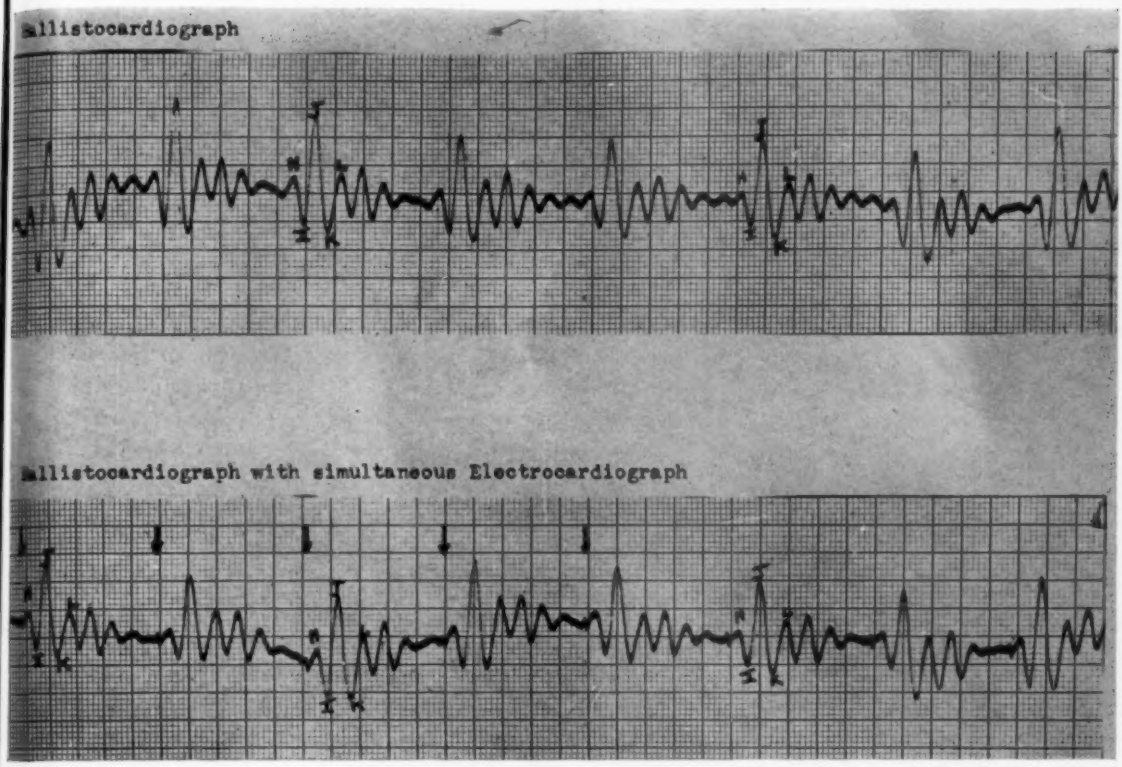

Fig. 3.—Employing the simultaneous electrocardiogram and ballistocardiogram at 7,500 ohms, the lower tracing shows no significant distortion of the ballistocardiographic waves as compared to the upper tracing taken on the same subject.

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A STUDY OF THE VOLUME-TIME COURSE OF THE PULSE WAVE OF THE FINGER TIP

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THE plethysmographically recorded volume pulse wave of the finger or toe tip represents a trace of change in volume with time. The changes in volume may be of several types.[1] Although some aspects of the concepts presented hereafter may apply to all of these volume waves, this report is concerned primarily with the pulse wave associated with each heart beat.

The maximum amplitude and configuration are the main characteristics of the volume pulse which have received attention. The rate of change in volume with time of the pulse of the finger and toe tip has not been observed in detail. Although the completed record of the volume pulse is a presentation of volume-time course, the observer usually is not fully aware of the temporal variations in volume. Furthermore, disease processes within the cardiovascular system result in alterations in the time course of the volume pulse. This report is concerned with certain aspects of variations in velocity and acceleration in volume or mass of blood in the finger tip of man with a normal cardiovascular system. Selected disease processes and reactions to stimuli are also presented for comparison.

METHOD

The subjects rested comfortably in a hospital-type bed in an air-conditioned room for thirty minutes before recordings were obtained. Changes in volume of the tips of the index fingers and second toes were recorded with a sensitive plethysmograph.[2] Details of the method of study have been described previously.[2] The contralateral parts were employed as controls or for duplication, depending upon the circumstances of the experiment.

Various stimuli or factors which are known to vary the flow of blood through the tips of the fingers and toes were employed in normal and diseased subjects, that is, a hot and humid environment, cold environment, and gravity. The abnormal states of the cardiovascular system which were studied included coarctation of the aorta, insufficiency of the aortic valve, stenosis of the aortic valve, and cirsoid aneurysms.

Selected pulse waves were enlarged by means of a projection lantern and were traced on Cartesian coordinate paper. These traces were then differentiated

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three successive times, and the respective plots of the derivatives were obtained. Although the plethysmograph[2] is not physically perfect, it proved to be satisfactory for the analyses made and the interpretations obtained.

THEORETIC CONSIDERATIONS

Before results can be adequately presented, it is necessary to give certain aspects of pulse wave proper consideration. The volume pulse wave (Fig. 1,*A*) associated with each heart beat and recorded plethysmographically represents the difference (in volume) with time between the volume of blood flowing into the part and that escaping from it (Fig. 1). For example, with each systolic ejection of blood from the heart a mass of blood is delivered to the tissues of the body; the tip of the finger or toe receives a share of this mass of blood. Over any period of time a theoretic basal volume of blood is flowing into and out of the part enclosed in the plethysmographic cup (Fig. 1). The theoretic basal volumes of blood flowing into and out of the part are equal. From experimental observation it seems doubtful that such a state of equal inflow and outflow exists for more than a fraction of a second. Nevertheless, for illustrative purposes only,

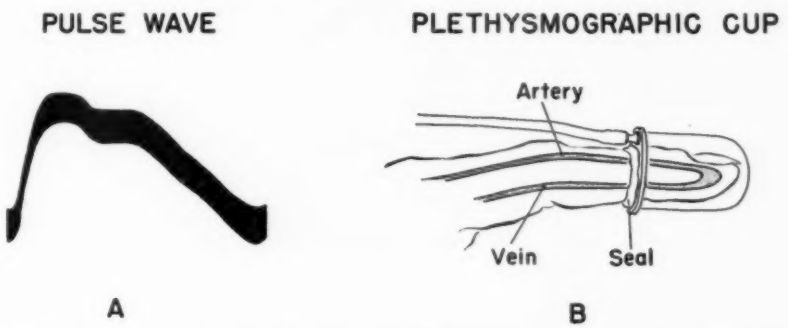

Fig. 1.—*A*, Average normal volume pulse wave of the finger tip. *B*, Diagram of plethysmographic cup on finger tip with schema of vascular "loop."

these theoretic basal volumes will be assumed to exist. When the share of blood ejected from the heart to the tip of the finger reaches the part enclosed in the plethysmographic cup, the rate with which blood flows into the cup exceeds that with which it is escaping. Because of this difference, the finger tip swells in volume and the upstroke of the pulse wave is inscribed. As previously stated, an ascending deflection of the plethysmogram indicates an increase in the volume of blood contained within the part. The part increases in volume at this time because the volume of blood being delivered to it per unit of time is larger than that which can simultaneously escape through the venous side, or the resistance to the flow of blood within the finger tip is so large that it is temporarily "dammed" within the part by the frictional resistance of the small vessels. The distensible vascular system expands to accommodate this extra blood. The location of the distention must be proximal to or within, and certainly not distal to, the site of resistance to flow. A knowledge of the details of distribution of friction within the vessel of the part is lacking. The arterioles, capillaries, venules, and shunting channels contribute unknown shares. Likewise, the relative contributions of

these vessels to the recorded volume change are also not known. Near the end of the systolic phase of the cardiac cycle and surely during the diastolic phase the volume of blood escaping from the part under study exceeds the volume entering. At this time the downstroke of the pulse wave is recorded. Thus the upstroke and downstroke of the pulse wave are a record of the algebraic sum of time-to-time volumes of inflow and outflow, or the pulse wave is a record of the time course of the volume difference between inflow and outflow of blood. For purposes of presentation, it will be assumed that the blood enters the part through the arterial system of vessels and escapes through the venous, although it is possible under particular circumstances for it to escape through the aterial side, as, for example, in aortic insufficiency.

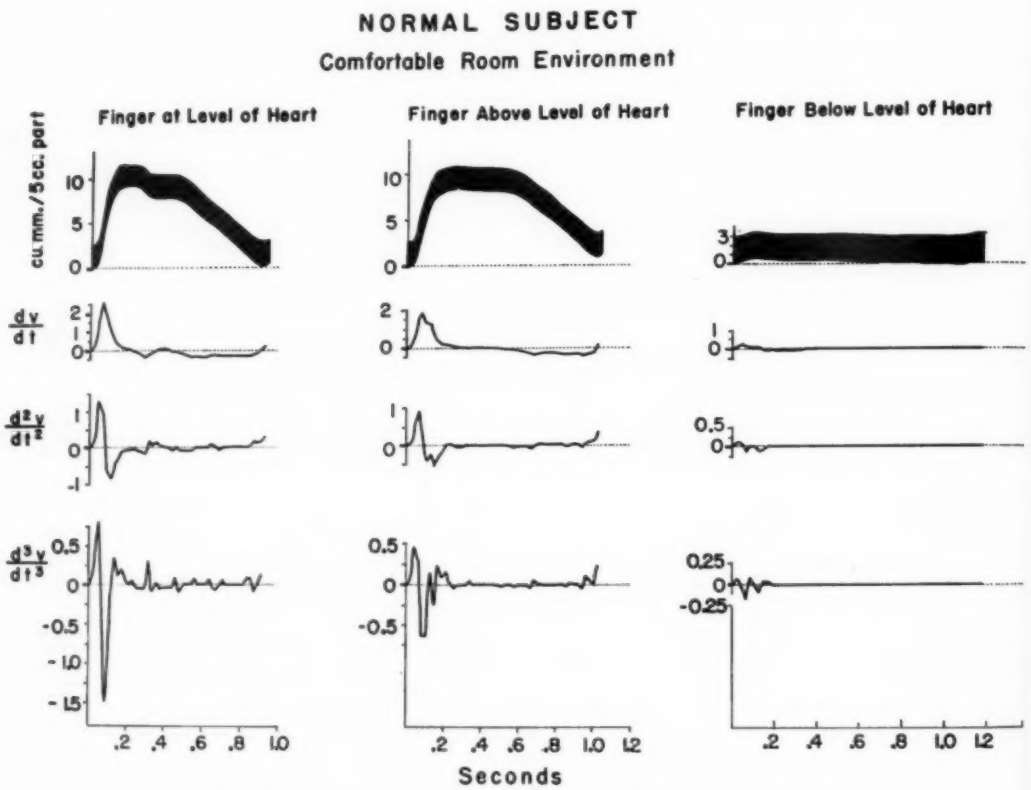

Fig. 2.—The volume pulse wave of the finger tip at heart level, above heart level, and below heart level for a normal subject in a comfortable environment. First, second, and third derivatives of the respective pulse waves are shown.

A plot of the *first derivative* $\frac{dv}{dt}$ of the volume pulse wave is a trace of the *rate* of change in the volume difference between volume inflow and outflow of blood to the part (Fig. 2). A plot of the *second derivative* $\frac{d^2v}{dt^2}$ of the volume pulse wave is a trace of *acceleration* or the rate of change of the rate of change in the volume difference between volume inflow and outflow of blood in the part

(Fig. 2). Although no known practical applications could be found for the *third derivative* $\frac{d^3v}{dt^3}$ in the literature, the trace of the third derivative (Fig. 2) was found to have a striking similarity to the ballistocardiogram.[3] The volume pulse waves were analyzed according to these concepts.

RESULTS

Normal Pulse Wave (Subject at Rest in a Comfortable Environment With Finger Tip at Heart Level).—The average normal *volume pulse wave* of the index finger tip has the well-known configuration shown in Fig. 2,*A*. The upstroke indicates a greater rate of flow of blood into the finger than out of it at that time. During inscription of the downstroke the rate of flow of blood out of the finger tip exceeded the flow into the finger tip. The shape of the trace indicates the time course of variations in the differences between the volume of flow into and out of the part. The variations among pulse waves are considerable.[1]

The plot of the *first derivative* of the pulse wave for the finger tip (Fig. 2), a curve of velocity or a rate of change of difference between inflow and outflow, shows that the maximum positive (rate of volume inflow exceeding rate of volume outflow) value is reached at about the half-way point of the upstroke of the volume pulse wave. The velocity curve rises quickly and then, after reaching its peak, descends quickly. The slope of the descending limb becomes extremely reduced at about the time the peak of the volume pulse is reached. This coincides in general with the phase of reduced injection of the cardiac cycle. The velocity curve assumes negative quantities immediately preceding the dicrotic notch, remaining negative except possibly when the upstroke of the dicrotic notch of the volume pulse wave is inscribed. The negative velocity values indicate the rate with which the volume of outflow exceeds the volume of inflow. Negative velocity values continue throughout the diastolic phase of the volume pulse wave, ending with the onset of the next systole (Fig. 2).

During the early part of the systolic phase of the volume pulse wave the *velocity* difference is greatest but relatively short in duration, whereas during the diastolic phase of the volume pulse wave the velocity difference is relatively small but its duration is long. Therefore, if there is no gain or loss in volume of the finger tip during a single pulse cycle, the positive and negative areas of the velocity curve should be equal (Fig. 2). Since the negative velocity portion of the curve tends to be horizontal during the diastolic phase of the volume pulse wave, this indicates that the velocity of outflow exceeds that of inflow by a fairly constant amount, and a steady state of flow difference tends to exist.

The plot of the *second derivative* of the volume pulse wave, a curve of *acceleration* or a rate of change of the rate of change in the difference between volume inflow and outflow, is shown in Fig. 2. A positive value on the acceleration plot indicates an increase in the rate with which the velocity of inflow exceeds that of outflow. The greater the positive value, the greater the rate of increase in rate of difference. The maximum value is obtained relatively early in the systolic phase of the volume pulse wave and definitely before the maximum value of difference between rate of inflow and outflow. The maximum negative value in the accelera-

tion curve is reached well before the peak of the volume pulse wave. It is evident from Fig. 2 that the acceleration curve tends to be horizontal throughout the diastolic phase of the volume pulse wave except for the period of the dicrotic notch.

The plot of the *third derivative*, which has no known physical connotation, is of interest in that it resembles the ballistocardiogram (Fig. 1).

Figs. 2 and 3 show the influence of gravity and of hot and cold environments on the volume pulse and the curves derived therefrom. When the finger is elevated above heart level, the maxima of the velocity and acceleration curves occur at approximately the same time in the pulse cycle as when the finger is held at heart level. Slight qualitative and quantitative variations in the velocity and acceleration curves are apparent. When the finger is held below heart level, much more definite changes were obtained. The small amplitude and lower slope of these curves are apparent.

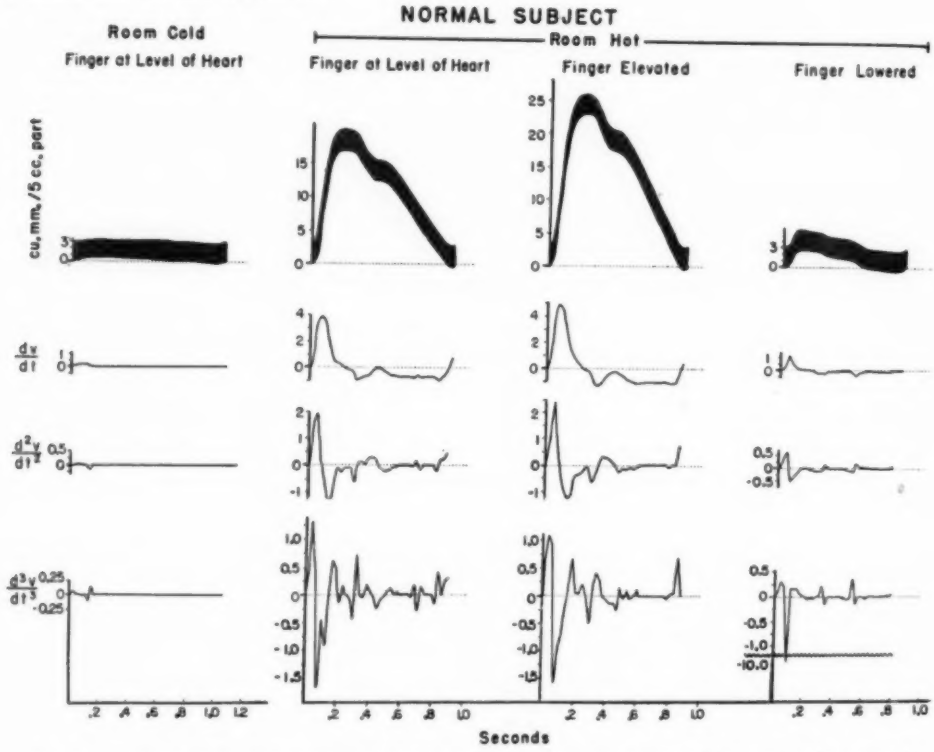

Fig. 3.—The volume pulse waves and their three respective derivatives of finger tip of a normal subject, showing the influence of environmental temperature and gravity.

When the finger was held at heart level and the room atmosphere was made cool (Fig. 3), the volume of pulsation, the maximum values of velocity and acceleration, and the amplitude of the curves of the third derivative were considerably reduced. In fact, they resembled closely the curves obtained when the finger was held below heart level with the subject in a comfortable atmosphere.

When the finger was held at the level of the heart and the subject was exposed to a hot environmental temperature (Fig. 3), the volume pulse wave was increased in amplitude. With the subject in a comfortable environment, the

velocity and acceleration curves attained maximum values when the finger was at heart level. In the hot environment the slopes of all curves of velocity and acceleration were steeper and of greater amplitude.

In the subject with coarctation of the aorta between the innominate and the left subclavian arteries, in the finger distal to the coarctation, the volume pulse and the maxima of the three derived curves were considerably smaller in magnitude than those observed for the side proximal to the point of constriction of the aorta (Fig. 4).

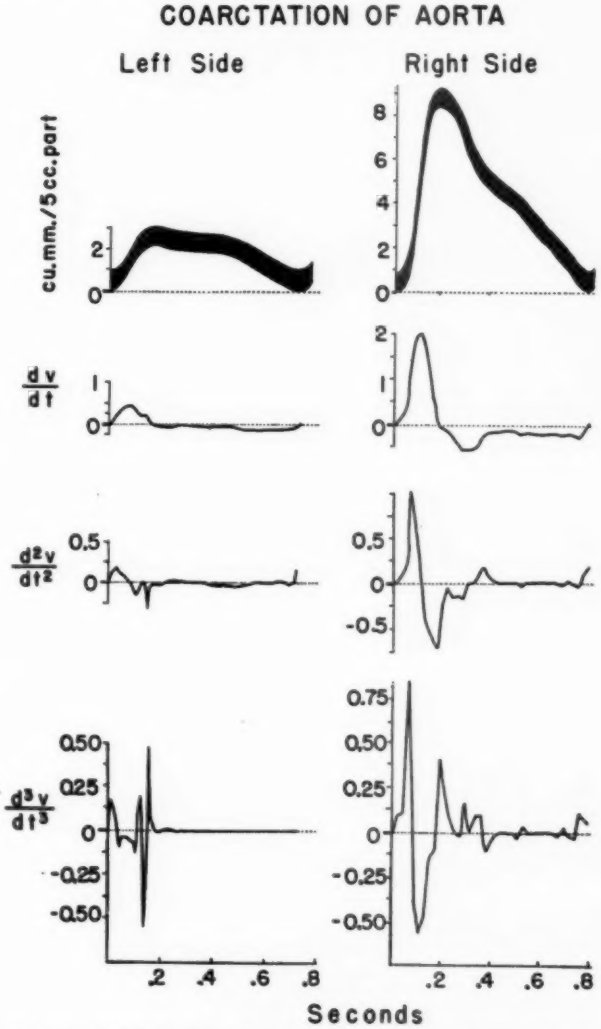

Fig. 4.—Illustration showing influence of coarctation on the volume pulse waves and their respective derivatives distal and proximal to the coarctation of the aorta.

Tracings of the volume pulse in a subject with aortic valvular insufficiency and in another subject with aortic valvular stenosis varied considerably in configuration from the normal, especially in the region of the dicrotic notch (Fig. 5). For example, in aortic stenosis the characteristic plateau pulse wave was seen

and in aortic insufficiency the pulse wave was more peaked. The normal is intermediate in magnitude and configuration (Fig. 2). Steepness of the curves of velocity and acceleration in aortic insufficiency is contrasted with the flat curves noted in aortic stenosis. Because of the small size or absence of the dicrotic notch in the volume pulse wave of the subjects with aortic stenosis and aortic insufficiency, the second positive deflection in the velocity and acceleration curves was extremely small or absent.

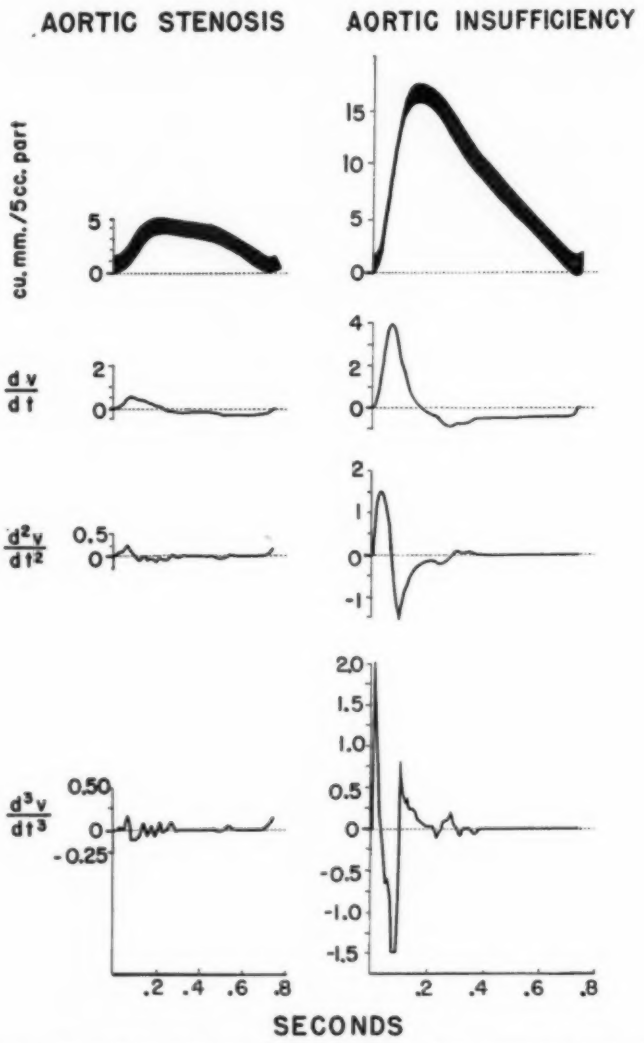

Fig. 5.—The volume pulse waves and respective derivatives in a patient with aortic stenosis and one with aortic insufficiency.

In the subject with cirsoid aneurysms involving the right arm and hand, striking differences appear in the curves obtained from the left and right fingers (Fig. 6). Except for slight variations in slope and amplitude, the curves of the left or uninvolved finger resembled the normal. The curves obtained from

the right or involved finger tip were strikingly different. The maximum amplitude and slope of the major deflection were considerably larger and steeper, and the maximum positive deflection occurred much earlier in the diseased finger than in the normal one. The rapidity with which major velocity and acceleration changes occurred was greater than any observed in this study.

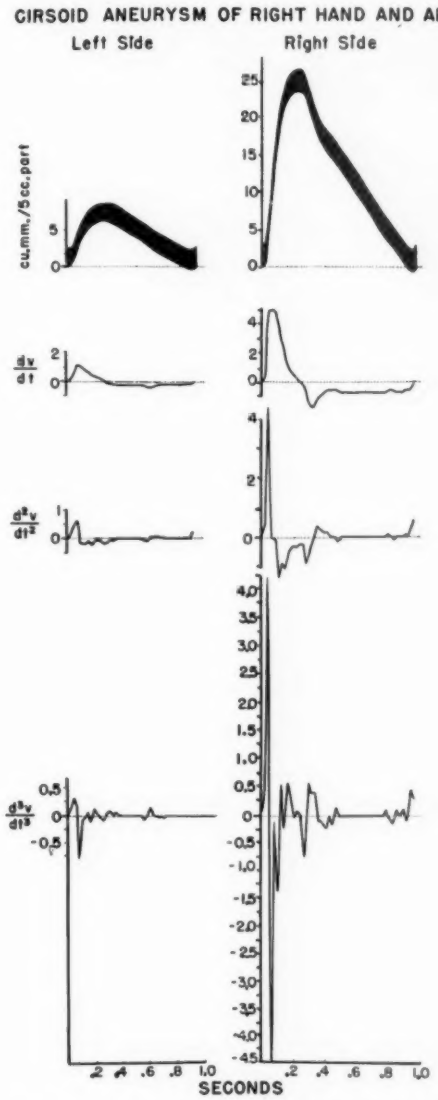

Fig. 6.—Illustration showing the influence of cirsoid aneurysm on the volume pulse wave and its derivatives.

DISCUSSION

These experiments showed that, distal to a coarctation of the aorta or aortic stenosis, the maximum values of the various derived curves were reduced below that for the normal finger at heart level with the subject in a comfortable room. When the subject was in a cold environment and the finger at heart level, the magnitudes of the various curves were also reduced. Elevation of the finger tip above heart level increased them, whereas lowering the part below the level of the heart decreased them. These observations indicate that the cold environment tended to reduce the maxima by local obstruction to flow, for example, by arteriolar constriction. On the other hand, when the finger was lowered, at least another factor was involved with reduction in the maximum magnitude of the pulse curves. This other factor is most likely concerned with engorgement and distention and tightening of the wall of the blood vessels of the finger tip by gravitational force. Therefore, when the blood is injected into the finger with systole, the maximum distention is limited and is reached early in the pulse cycle. The relative contributions of the distensibility factor and arteriolar constriction are unknown. Since the maxima were of the same magnitude for the cold environment and for the comfortable or hot environment with the finger below heart level, and since these maxima were reached later for the cold environment, the arteriolar constriction must have been less when the part was below heart level.

The early appearance and great magnitude of the maximum values of the various curves in the finger of the involved side in the subject with cirsoid aneurysm in whom the vessels were also engorged but not necessarily tightly distended indicate relatively less resistance to flow from the arterial to the venous side of the circulation than in any of the fingers observed, including conditions of elevation and warming.

Ordinarily, inspection of the volume pulse wave is not usually concerned with an analysis of the variations in velocity between volume inflow and outflow nor with differences in rate of change in rate of inflow and outflow. The velocity and acceleration curves presented depict these clearly. It is interesting to note that the maximum velocity difference occurs at about the end of the first quarter of the cardiac cycle, whereas the greatest acceleration difference occurs at about the end of the first sixth of the systolic phase of the cardiac cycle. Many more tracings must be studied to define more definitely these time relationships.

In all the acceleration curves, there was a large negative component. It began about the mid-point of the ascending deflection of the volume pulse wave and reached a maximum value well before the summit of the volume pulse wave.

The curve of the third derivative bears a remarkable resemblance to the ballistocardiogram. Like curves obtained from the experimental model of Starr and associates,[3] these lacked the I component usually recorded ballistocardiographically. Since the ascending limb of the volume pulse curve is S-shaped, the third derivative was similar to the ballistocardiogram without the I component. It is well to note that the curve of the third derivative of an ascending S-shaped

curve would have the appearance of the ballistocardiogram. The significance of the third derivative of the volume pulse wave is unknown. On the basis of the arguments presented by Starr and his associates for the ballistocardiogram of the model and of intact man, this third derivative might be considered an index of the forces concerned with the flow of blood through the finger tip, at least the energy-time (power) phenomena. It is difficult to integrate this in terms of recoil phenomena concerned with forces acting along the longitudinal axis of the finger tip. It is not possible to analyze successfully this plot of the third derivative in terms of forces related to friction, distention, and recoil of the blood vessels within the finger tip because of the complexity of the conditions. No attempt has been made in these studies to correlate these curves with measurements of the time course of volume flow.

These experiments were not intended to define the mean or the variations of the curves of the normal or any diseased state. Obviously, this would be of interest. These experiments were concerned primarily with analysis of the volume pulse wave in order to obtain the general pattern of the variations in velocity and acceleration, with time, of the blood volume inflow and outflow differences for the finger tip.

SUMMARY

The volume pulse waves of the index finger tip of normal man and subjects with selected diseases of the cardiovascular system were analyzed to study the time course of velocity and acceleration derived by successive differentiation of the pulse wave. These velocity and acceleration curves were described. The curve of the third derivative of the volume pulse wave was found to resemble remarkably the ballistocardiogram. Certain physiologic implications of these various curves were indicated.

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AN EXPERIMENTAL AND CLINICAL STUDY ON THE EFFECTS OF PROCAINE AMIDE (PRONESTYL*) ON THE HEART

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THERE have been several papers published describing the results obtained with procaine amide in different types of cardiac arrhythmias.[1-4] Most authors agree on its efficacy in ventricular arrhythmias and on its lesser therapeutic value in auricular arrhythmias. McCord and Taguchi[5] and Schaffer and associates[6] recently published the results they obtained with procaine amide on different types of auricular arrhythmias. From the experimental point of view, Wedd and associates[7] studied some of the pharmacologic properties of procaine amide in the turtle heart. We have also studied some effects of this drug on the hearts of dogs.[8]

In this paper, reference is made to the main observations encountered in our experiments with dogs and to our clinical experience in using procaine amide.†

METHOD

1. *Animal Experiments.*—Dogs anesthetized with sodium pentobarbital were used. The electrocardiographic records were made using the Grass electroencephalograph, Model III. In the experiments made with the chest unopened, standard leads were recorded. In experiments with opened thorax and artificial respiration, electrodes for stimulation and recording were placed on the epicardial surface of the auricles and ventricles. The electric excitability was measured by means of electric stimuli of constant duration (0.5 milliseconds) and variable intensity.[10] The speed of conduction was determined by measuring the difference between the time of activation of two points on the epicardial surface as measured by two recording electrodes placed in line with the stimulating electrodes and separated from them by a distance longer than 25 millimeters.[8] Procaine amide was administered through the femoral vein in all animals, either by a rapid intravenous injection or by a slow venoclysis.

In a first group of sixteen animals (Group A), the effect of procaine amide on the electrocardiogram, heart rate, rhythm, excitability, and speed of conduction in auricles and ventricles was studied. The drug was administered in most

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†The results given in this paper were read as preliminary reports to the "Sociedad Mexicana de Cardiología."[8,9]

instances by repeated intravenous injection of 0.025 to 0.050 Gm. per kilogram of body weight (Gm./kg.) and in some cases by venoclysis (0.100 to 0.150 Gm./kg.)* over about four hours.

In a second group of eight animals (Group B), we injected ouabain and procaine amide to study the combined action of these two drugs. The amounts of ouabain injected varied from 0.033 to 0.225 mg./kg.† This was followed by a dose of procaine amide, the effect of which had been previously tested on these animals. Some of these animals had received procaine amide some days before the experiment, being therefore suitable controls for the estimation of the effects of procaine amide alone.

2. *Clinical Observations.*—Thirty-seven patients suffering from different types of arrhythmias were given procaine amide either orally or intravenously. The initial oral dose varied from 0.50 to 1 Gm. every four to six hours. When the drug was injected intravenously, the dosage was varied according to the weight of the patient and from 0.3 to 1 Gm. was given at a rate of 0.2 Gm. per minute. Standard, unipolar limb, and precordial leads were used. When considered necessary, a bipolar precordial lead (Lian's lead) was recorded. In cases where the drug was administered intravenously a direct-writing electrocardiogram was obtained every thirty seconds.

In most cases of paroxysmal auricular tachycardia, a previous unsuccessful attempt had been made to control the disorder by means of the oculocardiac or the carotid sinus reflex. In two cases receiving quinidine, we waited for several hours before administering procaine amide. In two cases the arrhythmia had been induced by digitalis or ouabain.

We grouped the cases in this series according to the type of arrhythmia: (a) auricular extrasystoles and paroxysmal auricular tachycardia (fifteen cases); (b) paroxysmal auricular fibrillation and auricular flutter (six cases); (c) ventricular extrasystoles (eight cases), and (d) paroxysmal ventricular tachycardia (eight cases).

RESULTS

Animal Experiments.—

Group A. Effect of procaine amide on the physiologic properties of the heart: The animals which received procaine amide showed the following:

1. A decrease in sinus rate (Fig. 1, *I*) to 70 per cent of the control, four to five minutes after starting the injection.

2. A lengthening of the P-R interval (Fig. 1, *I*); widening of the P wave as well as of the P-R segment. This prolongation reached its maximum four to five minutes after starting the injection. The changes in the P-R as well as in the rate persisted thirty minutes after the injection.

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*The doses of procaine amide used were far beyond those used in clinical practice. What fundamentally interested us in this work, however, was to study the pharmacologic properties of the drug and the toxic changes produced by it on the electrocardiogram.

†It has been pointed out that "lethal doses" of ouabain and digitalin fluctuate about 0.1 and 0.4 mg./kg., respectively.[1]

3. A widening of the QRS complex, which usually did not adopt the morphology of a typical bundle branch block. The higher the rate of the pacemaker, the greater was the width of the QRS complex (delayed intraventricular conduction) (Fig. 3).

4. A prolongation of the Q-T interval which was greater than would be expected for the mere slowing of the rate.

5. Ventricular repolarization changes mainly secondary to the QRS changes.

Depending upon the amount of procaine amide injected and concomitantly with the effects mentioned above, the following disturbances in the cardiac rhythm were observed: (a) Sinus arrhythmia of variable degree; (b) sino-auricular block; (c) sinus standstill with permanent or intermittent nodal rhythm; (d) cardiac standstill or slow ventricular fibrillation. (Effects b, c, and d were observed whenever high doses of procaine amide were given, and they were sometimes reversible, except in the case of ventricular fibrillation.)

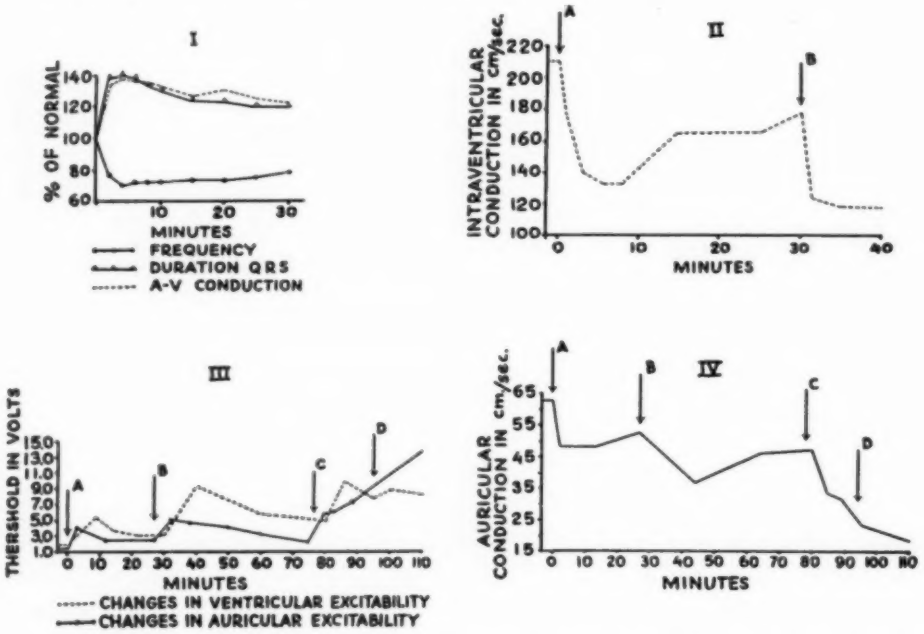

Fig. 1.—*I*, Percentage variations of rate, duration of QRS and P-R interval in animals with closed chest. The average figures of the control are arbitrarily set for 100 per cent. Moment zero was marked at the beginning of the intravenous injection of procaine amide.

II, Conduction velocity in the ventricle of one of the animals with open chest and denervated heart. Arrow *A* corresponds to the injection of 0.05 Gm./kg.; arrow *B* to the injection of 0.075 Gm./kg. of procaine amide.

III, Curves of excitability threshold in the auricle (continuous line) and in the ventricle (dotted line) in an animal with open chest and denervated heart. *A*, *B*, *C* and *D*, injections of procaine amide of 0.03, 0.05, 0.075, and 0.75 Gm./kg., respectively.

IV, Conduction velocity in the auricle of one of the animals with open chest and denervated heart after injection of different amounts of procaine amide. Arrows *A*, *B*, *C*, and *D* correspond to the injection of 0.05, 0.05, 0.05 and 0.025 Gm./kg. of the drug, respectively.

Six of these animals died after a total dose of approximately 0.150 Gm./kg. The animals that died as a consequence of lower doses were those with the greatest body weight. In these cases, the electrocardiographic signs recorded as terminal phenomena were usually as follows: (a) progressive widening of the QRS complex; (b) variable sino-auricular block; (c) auricular standstill with nodal escape or permanent nodal rhythm, and finally a slow ventricular fibrillation or cardiac standstill. When procaine amide was injected while the heart was electrically

stimulated at the auricle, the following were observed: (a) first-degree atrioventricular block; (b) second-degree atrioventricular block and Wenckebach-Luciani periods; (c) a phenomena analogous to Wenckebach-Luciani periods with cycles consisting of the following: (1) a short latent period between the registration of the stimulus and that of the response, with a normal auricular response; (2) a prolonged latent period between the registration of the stimulus and that of the response, with an abnormal auricular response; and (3) the registration of the stimulus alone, with no response.

In animals with denervated hearts, there was a parallel decrease in the excitability and in the speed of conduction, both in the auricles and in the ventricles (Fig. 1, *II*, *III*, and *IV*).

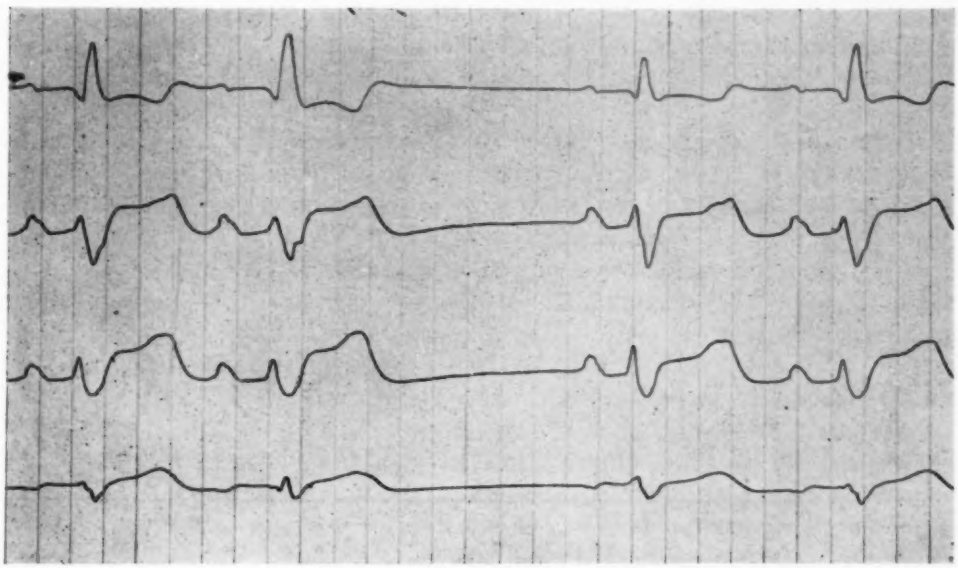

Fig. 2.—Simultaneous electrocardiographic tracings (L_1, L_2, L_3 and V_5) of an animal receiving toxic doses of procaine amide (0.150 Gm./kg. in one-half hour). It can be seen that damage has taken place on atrioventricular conduction, on intraventricular conduction, and on the pacemaker (sino-auricular block). Note also the diminution in the width of the QRS complex following the pause.

Group B. Effect of procaine amide in the heart of digitalized dogs: In this group the following results were observed:

1. During one hour of observation 0.05 mg./kg. of ouabain or equivalent doses of digitalis failed to produce either extrasystoles or damage to the intraventricular conduction. When electrocardiographic signs of digitalis effect (S-T sagging) appeared, the animals were killed by using high and repeated doses of procaine amide. The electrocardiographic changes observed were completely similar to those described above in animals intoxicated with procaine amide alone.

2. All the animals that received a single injection of 0.075 mg./kg. of ouabain or more showed, within fifteen minutes after the injection, the following signs of digitalis action: First- or second-degree atrioventricular block with aberrant intraventricular conduction, multifocal ventricular extrasystoles, atrioventricular dissociation with interference and, occasionally, paroxysmal ventricular tachycardia. Two of these dogs did not receive procaine amide and died in ventricular fibrillation about twenty minutes after ouabain was injected.

On the other hand, in the animals that had received procaine amide in doses from 0.025 to 0.050 Gm./kg., the extrasystoles disappeared for variable periods of time and regular sinus rhythm was re-established. In one animal intoxicated with ouabain, a first injection of procaine amide (0.050 Gm./kg.) re-established a regular sinus rhythm. A second injection of the same drug (0.075 Gm./kg.), administered forty-five minutes later, induced ventricular extrasystoles and ventricular flutter. The animal recovered from these disturbances but they reappeared when a third dose of procaine amide (0.075 Gm./kg.) was injected.

The fractional doses of procaine amide not only eliminated the ventricular extrasystoles induced by ouabain intoxication but, paradoxically, sometimes improved the atrioventricular conduction or the intraventricular conduction impaired by ouabain, probably because of the decrease in sinus rate (see Discussion). In this way animals survived longer than would be expected for the dose of ouabain employed.

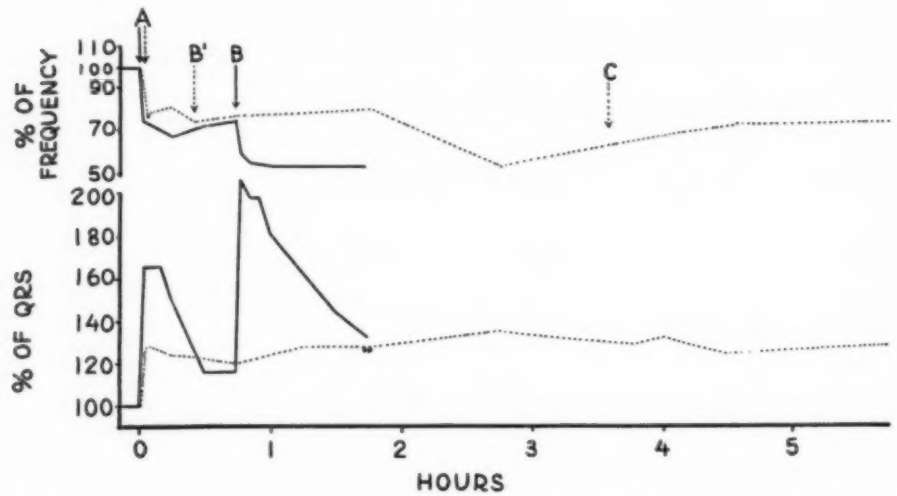

Fig. 3.—Percentage variation in the heart rate and in duration of QRS in two dogs of similar weight injected with a total dose of 0.125 Gm./kg. of procaine amide. One of them (continuous line), received the total amount in two doses (0.05 and 0.075 Gm./kg., respectively). The other (dotted line) received a dose of 0.025 Gm./kg. in a single dose (arrow *A*) and 0.100 Gm./kg. in slow intravenous drip between *B'* and *C*. Note that with both methods, similar maximal effects are obtained on heart rate whereas QRS widening (intraventricular conduction disorder) is greater with single doses than with slow intravenous drip.

In one of the dogs intoxicated with 0.075 mg./kg. of ouabain, extrasystoles likewise disappeared with procaine amide when this drug was given in slow venoclysis. This was the only animal that survived. The venoclysis was administered during ten hours and the speed of administration was adjusted to the needs of the moment. Fifteen days after this experiment, the same animal died of ventricular fibrillation in spite of the administration of 0.025 Gm./kg. of procaine amide in a single dose, just after a similar dose of ouabain was administered. Finally, in another animal that received 0.400 Gm./kg. of procaine amide in fractioned doses given during a period of four hours, a dose of 0.125 mg./kg. of ouabain was tolerated without the appearance of extrasystoles.

Clinical Study in Human Beings.—

Clinical Data.—In general, the electrocardiographic effects of procaine amide appeared within the first hour after oral administration. When procaine amide was administered orally or injected at the rate of 0.200 Gm. per minute, no marked fall in blood pressure was observed. The higher the basal blood pressure, the more marked was the fall observed. Some patients receiving the drug intravenously complained of certain side effects, such as bitter taste or a blushing sensation. When the drug was administered by mouth, two patients complained of insomnia, anorexia, and nausea. (Table I.)

1. *Group With Paroxysmal Auricular Tachycardia and Auricular Extrasystoles.* (*Patients 1 to 15*).—In ten of fifteen patients suffering from paroxysmal auricular tachycardia, the oculocardiac reflex and pressure of the carotid sinus failed. Only Case 10 showed transitory sinus rhythm but soon afterward the paroxysmal auricular tachycardia was re-established. In six cases (Cases 2, 3, 5, 7, 8, and 15), the use of procaine amide produced the disappearance of the ectopic rhythm, re-establishing a sinus rhythm (Fig. 4). In the cases in which sinus rhythm was not re-established, a variable depression in the rate of the ectopic focus and some widening of the QRS complex appeared. Both phenomena were more readily observed when the drug was given intravenously (Cases 4, 6, 9, and 11). (Fig. 5.)

In one case, auricular extrasystoles disappeared with an oral dose of 1 Gm. every four hours. In another case the auricular extrasystoles did not disappear with the administration of quinidine. Later on, these extrasystoles cleared up following treatment with digitoxin.

2. *Group With Paroxysmal Auricular Fibrillation and Auricular Flutter.* (*Patients 16 to 21*).—Case 16 changed to flutter, then to sinus rhythm (Fig. 6). In another patient with paroxysmal auricular fibrillation (Case 17) the administration of procaine amide had to be stopped, because of the presence of nausea and vomiting. This was a woman patient with a definite psychoneurotic background. The patient in Case 20 had received digitalis in toxic doses. She presented bigeminal extrasystoles. On the second day of administration of procaine amide (0.50 Gm. every four hrs.), she died suddenly, before an electrocardiographic record could be obtained. Two of the patients presenting auricular flutter (Cases 18 and 19) became worse after the administration of procaine amide, passing from a 2:2 atrioventricular response to a 1:1 response. At the same time, the disturbances of the intraventricular conduction increased (Fig. 7). The patient in Case 21 was thought to be suffering from paroxysmal auricular tachycardia, but after the injection of 0.50 Gm. of procaine amide it was realized that the case was one of auricular flutter. The ventricular rate having increased, the drug was discontinued.

3. *Group With Ventricular Extrasystoles.* (*Cases 22 to 29*).—In seven of the eight patients, cardiac rhythm became normal. Only in one of them (Case 27) did the extrasystoles persist despite the administration of 1 Gm. of the drug every four hours (the extrasystoles were unifocal and apparently located high in the septum). Quinidine also failed but the extrasystoles disappeared during the course of digitalis treatment. Case 26 (Fig. 8) was a woman patient,

TABLE I.

CASE	AGE (YRS.)	DIAGNOSIS	DOSE OF PROCAINE AMIDE	APPEARANCE OF EFFECT	RESULTS	FURTHER COURSE
			PAROXYSMAL AURICULAR TACHYCARDIA			
1	25	P.A.T.	1st: 0.75 Gm. 2nd: 0.75 Gm.	45 min.	Rate diminished	6 c.c. of digilanid
2	47	R.H.D.	1 Gm.	30 min.	N.S.R.	
3	60	R.H.D.	7 c.c. (0.7 Gm.)	2 min.	N.S.R.	V.E.
4	38	H.Cv.D.	1st: 5 c.c. 2nd: 2.5 c.c.	2 min.	Rate diminished	Quinidine
5	47	H.Cv.D. W.P.W.	5 c.c. (0.5 Gm.)	1.5 min.	N.S.R.	No crises with 0.50 Gm. every 4 hrs.
6	16	R.H.D.	5 c.c. (0.5 Gm.)	1 min.	Rate diminished	No effect with acetylcholine
7	44	H.Cv.D.	1 Gm.	1 hour	N.S.R.	
8	49	H.Cv.D.	1 Gm.	45 min.	N.S.R.	
9	32	W.P.W.	7.5 c.c. (0.75 Gm.)	2 min.	Rate diminished	6 c.c. of digilanid; 4 c.c. of lanatoside C
10	53	H.Cv.D.	1st: 0.75 Gm. 2nd: 0.75 Gm.	45 min.	Rate diminished	
11	38	W.P.W.	1st: 1 Gm. 2nd: 1 Gm.	50 min.	Rate diminished	Acetylcholine 0.04 Gm.
12	58	M.In.	8 c.c. (0.8 Gm.)	2 min.	Rate diminished	Quinidine
13	65	As.H.D. A.E.	1 Gm. every 4 hrs.		N.S.R.	Drug discontinued
14	54	As.H.D. A.E.	1 Gm. every 4 hrs.		None	Digitalin Nativelle
15	56	As.H.D. P.A.T.	1 Gm.	1 hour	N.S.R.	
			PAROXYSMAL AURICULAR FIBRILLATION AND AURICULAR FLUTTER			
16	27	R.H.D. P.A.F.	2.5 Gm. in 12 hrs.	1 hour	N.S.R.	
17	23	R.H.D. P.A.F.	0.50 Gm.	1 hour	Partial	Medication stopped
18	14	R.H.D. A. Fl. 2:1	5 c.c. (0.5 Gm.)	1.5 min.	1:1 flutter	A.F.
19	49	As.H.D. P.A.Fl.	0.75 Gm. every 4 hrs.		Flutter 1:1	N.S.R. with quinidine
20	26	R.H.D. A.F.	0.75 Gm. every 4 hrs.	1 hour	V.E. disappeared	Sudden death
21	52	R.H.D. P.A.Fl.	5 c.c. (0.5 Gm.)	2 min.	Rate of Fl. diminished	N.S.R. with quinidine
			VENTRICULAR EXTRASYSTOLES			
22	27	R.H.D.	1 Gm. and 0.5 Gm. every 4 hrs.		N.S.R.	
23	50	As.H.D.	0.75 Gm. every 4 hrs.	45 min. after 0.75 Gm.	N.S.R.	Insomnia, anoxia
24	48	H.Cv.D.	5 c.c. + 5 c.c. (1 Gm.) in 250 c.c. i.v.	1.5 min.	N.S.R.	
25	53	M.In.	4 c.c. (0.4 Gm.)	2 min.	N.S.R.	With 0.75 Gm. every 4hrs., no extrasystoles
26	40	Digitalis intoxication	0.5 Gm. every 4 hrs.	45 min.	N.S.R.	P.V.T. and V.F.
27	26	R.H.D. Digitalis intoxication	0.5 Gm. every 4 hrs.	30 min.	A.F. persisted	Sudden death
28	60	R.H.D.	1 Gm. every 4 hrs.		None	V.E. disappeared with digitalis
29	17	N.H.	0.75 Gm. every 4 hrs.		N.S.R.	

TABLE I (CONT'D)

CASE	AGE (YRS.)	DIAGNOSIS	DOSE OF PROCAINE AMIDE	APPEARANCE OF EFFECT	RESULTS	FURTHER COURSE
			PAROXYSMAL VENTRICULAR TACHYCARDIA			
30	55	As.H.D.	10 c.c. (1 Gm. in 200 of saline)		None	N.S.R. with intravenous quinine
31	40	Essential P.V.T.	5.5 c.c. (0.55 Gm.)	2 min.	N.S.R.	?
32	56	M.In.	0.75 Gm. every 4 hrs.	30 min.	N.S.R.	N.S.R. with 0.50 Gm. every 4 hrs.
33	32	Recurrent P.V.T.	3 c.c. (0.3 Gm.)	2 min.	N.S.R.	
34	8	Patency of ductus	3 c.c. (0.3 Gm.) + 4 c.c. (0.4 Gm.)	3 min.	N.S.R.	No more crises
35	38	Constrictive pericarditis	4 c.c. (0.4 Gm.)	2 min.	N.S.R.	No more crises
36	9	Tetralogy of Fallot	2 + 3 c.c. (0.5 Gm.)	3 min.	N.S.R.	
37	64	M.In.	3 c.c. (0.3 Gm.)	2 min.	N.S.R.	No more crises

N.H. = Normal heart
R.H.D. = Rheumatic heart disease
N.S.R. = Normal sinus rhythm
As.H.D. = Arteriosclerotic heart disease
H.Cv.D. = Hypertensive cardiovascular disease
M.In. = Myocardial infarction
W.P.W. = Wolff-Parkinson-White syndrome
P.A.T. = Paroxysmal auricular tachycardia
P.A.F. = Paroxysmal auricular fibrillation
A.Fl. = Auricular flutter
A.F. = Auricular fibrillation
V.E. = Ventricular extrasystoles
A.E. = Auricular extrasystoles
P.V.T. = Paroxysmal ventricular tachycardia
V.F. = Ventricular fibrillation
P.A. Fl. = Paroxysmal auricular flutter

40 years old, who was extremely ill, suffering from chronic cor pulmonale and bigeminal rhythm due to multifocal ventricular extrasystoles produced by digitalis intoxication. (She had taken 0.25 mg. of ouabain every other day, for an unknown period of time. She was also receiving 20 drops daily of digitalin, during four days.) The first dose of 0.750 Gm. of procaine amide, orally, cleared up the extrasystoles one hour after the administration of the drug, but the rapid activity of the auricle persisted (Fig. 8,*C*). Seven hours after this first dose, the extrasystoles reappeared and a second dose of 0.750 Gm. was again effective. Thereafter, the patient received 0.50 Gm. every four hours as a maintenance dose. The electrocardiogram taken the following morning at 8:00 A.M. (one hour after the last dose of procaine amide) showed a regular sinus rhythm. Owing to an error, the patient did not receive the 11:00 A.M. dose and at noon the patient suddenly had a convulsion, loss of consciousness, and absence of heart sounds. She recovered through the application of artificial respiration and the heart was heard beating regularly at a rate of 110 per minute. Fifteen minutes later she had another convulsion. Immediately afterward, an electrocardiogram was taken (Fig. 8,*G*) and a minute later a third attack occurred (the tracing showed ventricular flutter) (Fig. 8, *H*, *I*, and *J*), and the patient died.

4. *Group With Ventricular Paroxysmal Tachycardia.* (*Cases 30 to 37*; *Fig. 9*).—In five of eight patients (Cases 31, 32, 33, 34, and 37) paroxysmal ventricular tachycardia was eliminated following the administration of procaine amide. Cases 34, 35, and 36 presented crises of paroxysmal ventricular tachycardia during surgical interventions on the heart. One-half hour before the operation the patients received prophylactic doses of procaine amide of about 0.2 Gm. The first two cases reverted to sinus rhythm after the injection of procaine amide was repeated. In Case 36 the results obtained with the drug were doubtful, since recurring crises of paroxysmal ventricular tachycardia appeared every time that the heart was handled (pericardectomy). In Case 30, the patient did not show any response to the drug in different doses; some hours later a sinus rhythm reappeared after the use of intravenous quinine.

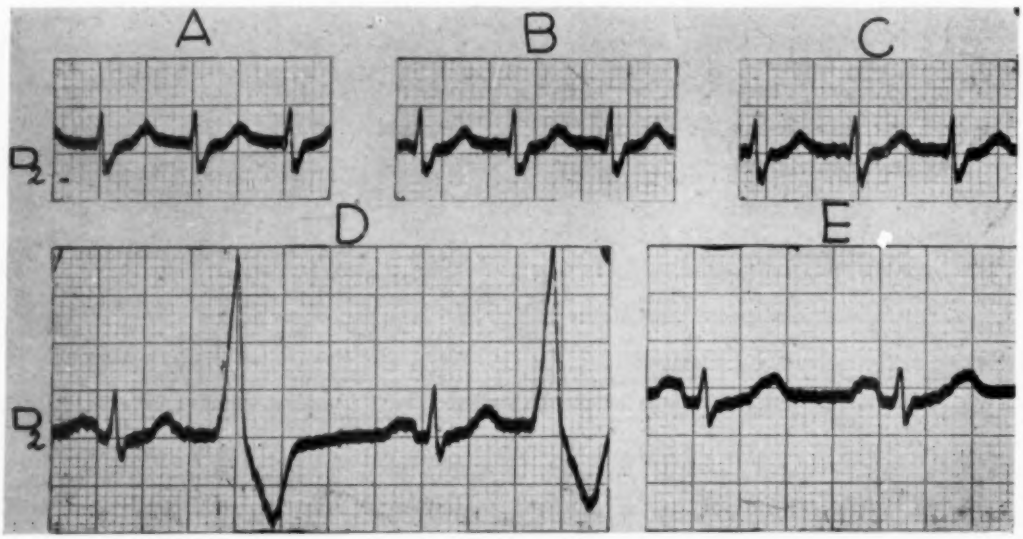

Fig. 4.—Supraventricular paroxysmal tachycardia. (Case 3.)
A, Control. *B*, One-half minute after the beginning of the injection of procaine amide (0.700 Gm.). *C*, One minute after the beginning of the injection. *D*, One and one-half minutes after the beginning of the injection. Sinus rhythm has been restored and bigeminal ventricular extrasystoles have appeared. *E*, Five minutes after the injection, regular sinus rhythm.

DISCUSSION

From the results obtained in the animal experiments, conclusions can be drawn about the effects of procaine amide on the following properties of the heart: automatism, excitability, and speed of conduction.

1. By depressing the sinus automatism, procaine amide is capable of producing sinus bradycardia, interference dissociation, sino-auricular block, and even sinus arrest with intermittent or permanent nodal rhythm. This action on the sinus rhythm is mainly due to a direct effect on the sino-auricular node, since it is produced also in the denervated heart. Procaine amide also depresses ectopic rhythms experimentally produced by ouabain or spontaneously appearing in clinical cases of both auricular and ventricular origin.

Adequate doses of procaine amide depress the excitability of both the auricle and the ventricle; therefore, its intravenous or local injection is of promise in the surgery of the heart.

The speed of conduction is diminished both in the auricles and in the ventricles. This effect can be observed only by injecting more than 0.05 Gm./kg. The lengthening of the P-R interval may be due in part to a delayed conduction in the auricular muscle and in part to a delay in the atrioventricular conduction. The observed delay of intraventricular conduction is directly related to the speed with which procaine amide is injected. Equal doses of procaine amide administered in a single intravenous injection or in slow venoclysis may produce a similar depression of sinus rate, but a very different degree of delay in the intraventricular conduction (Fig. 2).

Despite the lack of a direct and quantitative determination of the refractory period, the phenomena observed in the animal injected with procaine amide, while the auricle was electrically stimulated, indicates a prolongation of the refractory period in the auricle as well as in the atrioventricular junction.

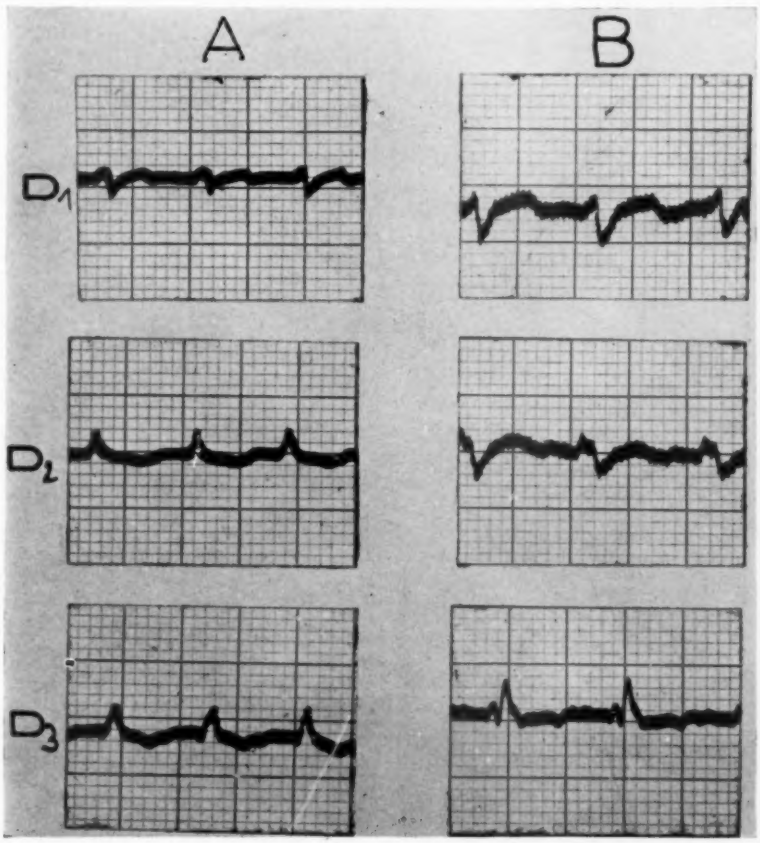

Fig. 5.—Paroxysmal auricular tachycardia. (Case 6.)
A, Control. Observe the auricular waves overlapping with the end of the T wave. *B*, Five minutes after the beginning of the injection of 5 c.c. (0.500 Gm.) of intravenous procaine amide. The rate of the ectopic focus has diminished and QRS has widened (right bundle branch block morphology).

2. The action of procaine amide can only be understood when it is realized that some of the properties of the heart are not independent but interrelated. For instance, the higher the rate of the supraventricular pacemaker, the more evident is the damage to the atrioventricular conduction. This is why a second-degree atrioventricular block was observed only in cases in which the auricular rate was artificially maintained high by means of a stimulator, while in cases of spontaneous auricular or sinus rhythms the pacemaker was depressed by procaine amide and only a first-degree atrioventricular block was observed or no disturbances were registered in the atrioventricular conduction. Similarly, the higher the ventricular rate, the greater is the damage

to the intraventricular conduction. This is why it was easy to observe marked QRS enlargement in cases in which procaine amide was not sufficient to depress importantly the rate of ventricular activation, as in some paroxysmal auricular tachycardia (Fig. 5), auricular flutter (Fig. 7), digitalis intoxication with extrasystoles, etc. Certain animals, intoxicated with digitalis, presenting delayed atrioventricular conduction and abnormal intraventricular conduction, showed an improvement of atrioventricular conduction and of the intraventricular conduction when procaine amide was administered. This was probably due to a diminution in the rate of the pacemaker. Possibly, because of this, procaine amide, when rapidly administered, is capable of producing important widening of the QRS complex since great concentrations of the drug are obtained without having,

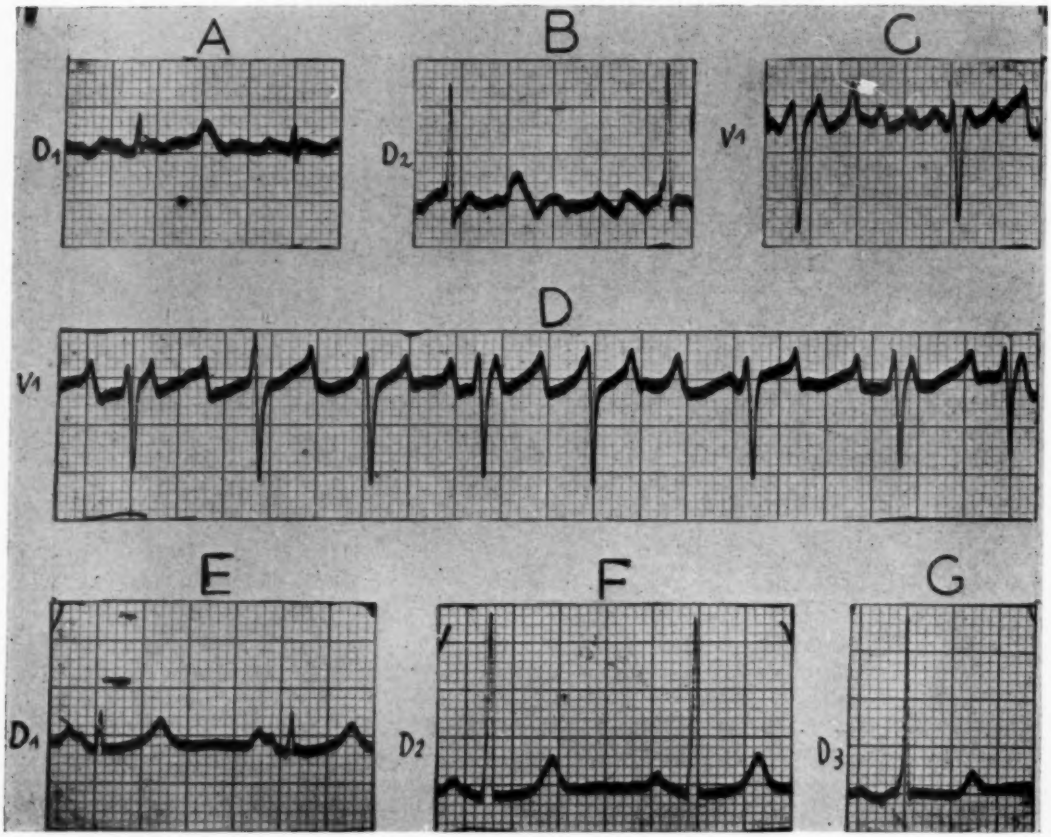

Fig. 6.—Paroxysmal auricular fibrillation. (Case 16.)
A, *B*, and *C*, Controls. *D*, One hour after the ingestion of 0.500 Gm. of procaine amide. The auricular waves have become regular and slower. Appearance of impure flutter with irregular ventricular response (2:1 and 3:1). *E*, *F*, and *G*, Controls after further procaine amide administration (2.5 Gm. total dose). There is a regular sinus rhythm.

at the same time, an equally important depression of the pacemaker. On the other hand, the increased damage to the intraventricular conduction increases the probabilities of an outburst of abnormal ventricular automatism, perhaps because it facilitates some re-entries in the ventricular tissue. Thus procaine amide, a drug which may suppress ventricular ectopic foci, may also induce a paroxysmal ventricular tachycardia or may induce ventricular fibrillation. This latter may be seen during digitalis intoxication, where intraventricular conduction is radically altered, both because of the direct action of digitalis and procaine amide and because of the indirect damage produced by the high ventricular rate.

3. Clinical considerations: The results observed after the administration of procaine amide in cases of arrhythmias of auricular origin are clinical evidence of the action of the drug upon the auricular muscle. However, we believe that procaine amide is not the drug of choice for paroxysmal auricular tachycardia, which usually responds favorably to acetylcholine or its derivatives. Only in those cases where acetylcholine fails (lack of response or recurrence of the arrhythmia) or in those where a contraindication to it exists (patients with low blood pressure, etc.), should procaine amide be considered.

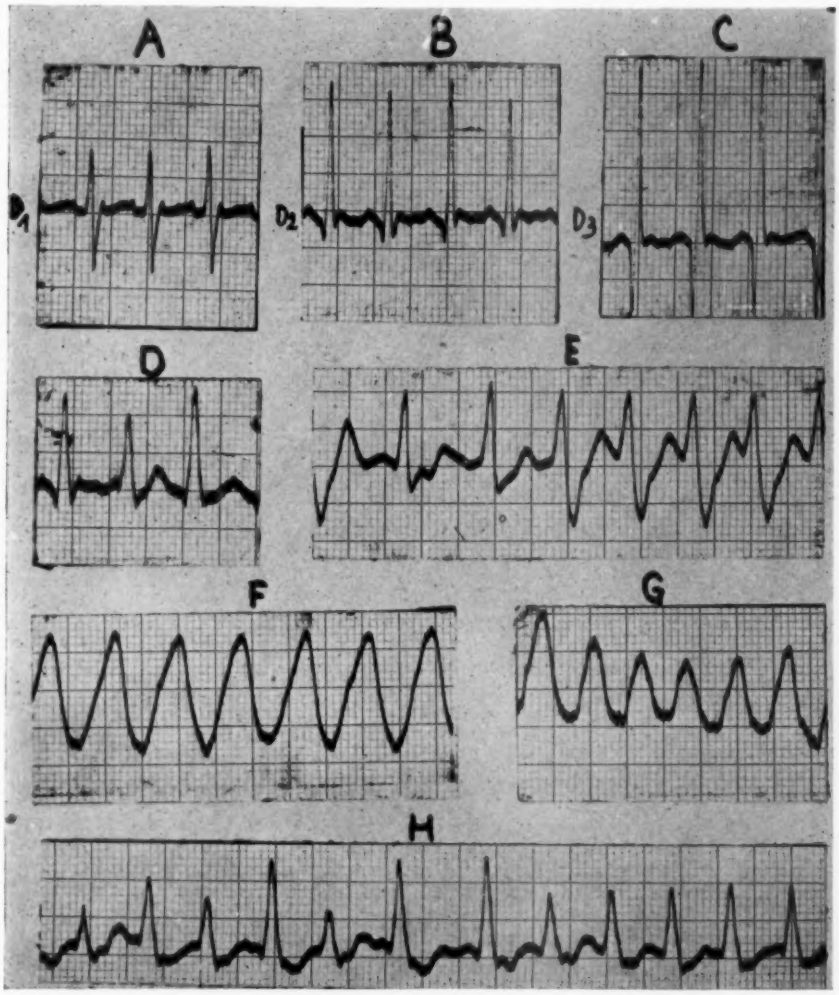

Fig. 7.—Auricular flutter with 2:1 atrioventricular conduction. (Case 18.)

A, *B*, and *C*, Controls. *D*, Lead II one minute after the beginning of the injection of 5 c.c. (0.500 Gm.) of procaine amide. QRS widening. Flutter wave is slower. *E*, Two and one-half minutes after the beginning of the injection. Note the alternating intraventricular conduction. The flutter wave has become even slower and there is a 1:1 atrioventricular response, due to the slight action of the drug on atrioventricular conduction. *F*, One minute after *E*; intraventricular conduction has been further affected, in part due to the direct action of procaine amide and in part due to the rapid activation of the ventricles. The tracing might seem, at first, that of a paroxysmal ventricular tachycardia, but due to the progressive damage observed on intraventricular conduction and due to the fact that the ventricular rate is the same as that of the flutter wave at *E*, we believe it is rather a 1:1 auricular flutter with aberrant ventricular conduction. *G*, One minute after *F*; the activation rate of the ventricles has increased. It may result from a paroxysmal ventricular tachycardia (favored by the damage of ventricular conduction together with the rapid activation of the ventricles) or to auricular flutter-fibrillation with aberrant ventricular conduction. In favor of this latter view is the fact that this patient later developed persistent auricular fibrillation. *H*, Seven minutes after the injection of procaine amide. There is auricular fibrillation or flutter-fibrillation.

In our cases of auricular flutter with 2:1 atrioventricular response and in others mentioned by Berry and associates,[12] procaine amide produced unfavorable results due to three main factors: (1) A decrease in the rate of the flutter; (2) a meager effect of the drug on the atrioventricular conduction, and (3) some damage to the intraventricular conduction. The rate of the flutter wave being more depressed than the atrioventricular conduction, there is a tendency toward

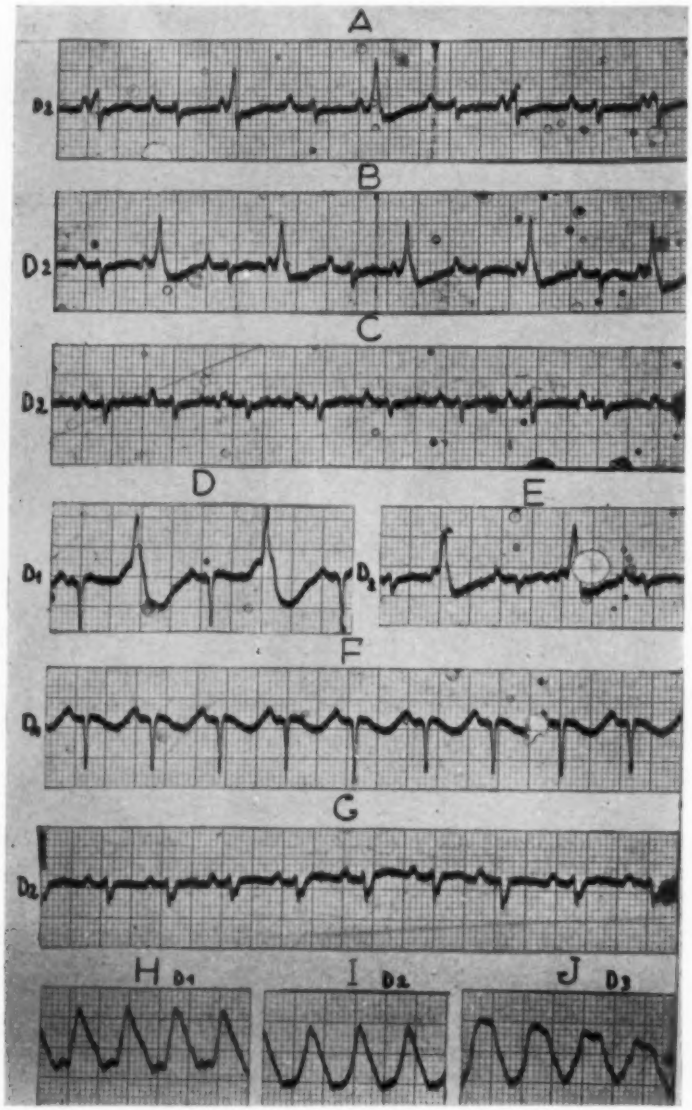

Fig. 8.—Sinus tachycardia and ventricular extrasystoles due to digitalis intoxication. (Case 26.) *A*, Control. Ventricular extrasystoles are bigeminal and multifocal. Due to the shortness of P-R (for the extrasystoles), the likelihood of atrioventricular conduction may be discarded. *B*, Forty-five minutes after the ingestion of 0.75 Gm. of procaine amide, bigeminal extrasystoles appear but they all arise from a single focus. *C*, One hour later. Regular sinus rhythm. *D* and *E*, Seven hours after procaine amide. Extrasystoles reappeared. *F*, Control at 8:00 A.M. next day after the beginning of the treatment (see text). Extrasystoles have disappeared. *G*, One minute before *H*, *I*, and *J*. Note increased duration of QRS compared to *C*. *H*, *I*, and *J*, Paroxysmal ventricular tachycardia (see text), followed by sudden death.

a 3:2 or even a 1:1 atrioventricular response; this increases the rate of ventricular activation. One must keep in mind, on the other hand, that intraventricular conduction is damaged not only because of the increase in the myocardial concentration of procaine amide but by the increase in the rate of ventricular activation. Delayed intraventricular conduction plus increased rate of activation of the ventricles favor the appearance of ventricular ectopic foci (Fig. 7,*G*) or even of ventricular fibrillation.[18]

Our results in paroxysmal ventricular tachycardia or ventricular extrasystoles confirm the findings of other authors[2-4] who believe that procaine amide is the drug of choice in these cases because of its efficacy both orally and intravenously as well as its low toxicity.

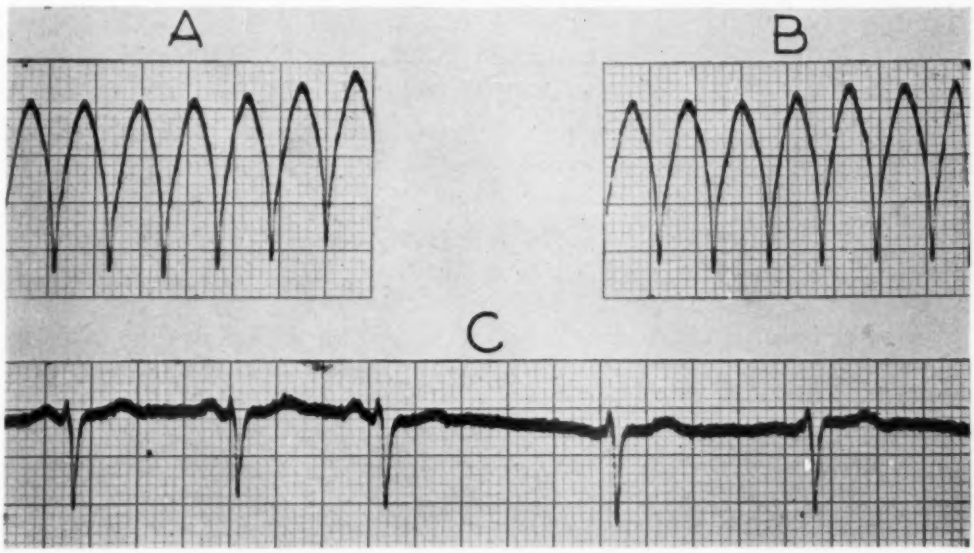

Fig. 9.—Paroxysmal ventricular tachycardia. (Case 33.)
A, **Control in Lead III.** *B*, **The same lead one minute after the injection of 3 c.c. (0.3 Gm.) of procaine amide.** *C*, **Three minutes after the beginning of the injection. Sinus rhythm followed by auricular standstill during which a nodal rhythm appears.**

Since the publication of the first studies on procaine amide, and in a recent paper,[13] different authors have considered that the use of procaine amide in arrhythmias produced by digitalis or its derivatives would not be contraindicated. On the other hand, Gold[15,16] pointed out the possible danger in administering simultaneously quinidine and digitalis and remarked that he has seen fatal cases in patients, as well as experimentally in dogs. Zapata-Díaz and associates[17] recently stated: "The association of drugs such as digitalis and quinidine or procaine, which have an antagonistic action on the automatism but act synergetically on the conductivity of the heart, involves certain risks, since there is the possibility of inducing ventricular ectopic foci, which might be of fatal consequences."

From what we observed in animals intoxicated with digitalis in whom procaine amide was injected, we wish to point out the following: (1) Adequate

doses of procaine amide, properly administered, eliminate for variable periods of time the extrasystoles produced by digitalis and make regular the cardiac rhythm, and (2) procaine amide given to digitalis-intoxicated dogs easily produces an accentuated disturbance in intraventricular conduction and contributes to the appearance of ventricular flutter or even ventricular fibrillation. For this latter to occur, it is usually required: (a) that digitalis produce a rapid ventricular rate,[14] due either to ventricular ectopic foci or to sinus tachycardia, (b) that digitalis produce damage to the intraventricular conduction,[14] and (c) that the beginning or the end of the action of procaine amide be sudden.

In our clinical series, the two patients who died during the administration of procaine amide were the only two suffering from digitalis intoxication. Kayden and associates[13] reported on fifteen cases of paroxysmal ventricular tachycardia. One of their fatal cases had a paroxysmal ventricular tachycardia which relapsed short after the injection of lanatoside C. The patient died while receiving procaine amide after only 145 mg. had been injected.

The observations made experimentally in dogs, the two fatal cases we had, and Kayden's case referred to above show that the association of digitalis and procaine amide is a dangerous one.

From what has been previously mentioned, the following clinical attitude in cases of digitalis intoxication is suggested: (1) In the presence of a mild intoxication, that is, a case in which digitalis has caused a bigeminated rhythm or an atrioventricular block of first or second degree, an expectant attitude is indicated. (2) If the severity of the intoxication (with multifocal extrasystoles, chaotic rhythm, or paroxysmal ventricular tachycardia) makes a fatal outcome likely, procaine amide would be used with the knowledge that a drug is being administered which, while capable of preventing ventricular fibrillation, can also favor the appearance of this disturbance if not properly used. It should be kept in mind that these accidents are less likely to occur if the myocardial concentrations of procaine amide are adequate to keep off the ectopic foci without considerably impairing intraventricular conduction. This could be effected by giving the drug by means of a slowly administered venoclysis with simultaneous electrocardiographic control. Once the arrhythmia is controlled, procaine amide should be maintained until digitalis is likely to be eliminated.

SUMMARY AND CONCLUSION

From the experimental study in animals and the clinical study in human beings on certain actions of procaine amide, the following conclusions can be drawn:

1. Procaine amide increases the threshold of excitability and slows down the speed of conduction both in the auricles and in the ventricles.

2. It shows little effect on the auriculoventricular conduction when the heart maintains sinus rhythm.

3. The impairment of atrioventricular and intraventricular conduction is greater when the rate of the pacemaker is higher.

4. Administration of procaine amide given in equal doses has a greater effect on intraventricular conduction when administered in a single intravenous injection than is slowly administered venocysis.

5. Procaine amide is effective on auricular disorders. It clears up auricular extrasystoles and supraventricular paroxysmal tachycardia, and it can slow down the rate of auricular fibrillation or flutter. Since paroxysmal auricular tachycardia responds favorably to acetylcholine or its derivatives, the use of procaine amide should be reserved for those cases in which acetylcholine is ineffective or contraindicated.

6. Procaine amide should be the drug of choice in cases of arrhythmias of ventricular origin (extrasystoles, ventricular flutter, and paroxysmal ventricular tachycardia). Since it is active either orally or intravenously, it should be administered by either route according to the severity of the case.

7. In cases of auricular flutter, the use of procaine amide is dangerous because it can lead to a 1:1 atrioventricular response with aberrant intraventricular conduction, eventually inducing ventricular flutter or fibrillation. In cases of paroxysmal auricular fibrillation, procaine amide may re-establish a sinus rhythm but it does not seem to be void of danger.

8. In the treatment of arrhythmias due to overdosage of digitalis or its derivatives, it should be kept in mind that while procaine amide can clear up ventricular extrasystoles produced by digitalis, its improper use can favor the occurrence of ventricular flutter or ventricular fibrillation. This danger may be reduced by giving procaine amide by a slowly administered venoclysis, checking constantly the electrocardiogram.

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AN EVALUATION OF ANTICOAGULANT THERAPY IN THE TREATMENT OF ACUTE MYOCARDIAL INFARCTION

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THE possibility that anticoagulants may be of value in the prevention and treatment of acute myocardial infarction was suggested by a series of animal experiments in which the incidence of artifically induced intravascular clots was observed to be dramatically reduced by the use of heparin.[1-4] In 1941 and 1942, heparin or Dicumarol was first used clinically in individual cases or in small series of cases of acute myocardial infarction.

The first American report concerned exclusively with the use of Dicumarol in acute coronary occlusion appeared in December, 1945, when Wright[5] described his experience with seventy-six cases. Between the time of that report and 1949, over twenty individual series of cases were published in the American literature. As reflected in these reports, the greatest experience with this means of therapy was obtained by Peters, Guyther, and Brambel[6,7] in Baltimore, by Nichol[8-10] in Miami, by Parker and Barker[11,12] at the Mayo Clinic, and by Wright and his associates[13-17] in New York. Although the early reports seemed consistently favorable, the results were in no instance based upon a sufficiently large series of properly controlled cases to warrant statistical analysis. These initial observations did, however, lead to the more extensive study carried out by the American Heart Association's committee for the evaluation of anticoagulants in the treatment of coronary occlusion with myocardial infarction.

This large-scale investigation[16,18,19] at sixteen leading hospital centers provided data for statistical analysis of 1,031 cases of acute myocardial infarction. Of this number, 442 received conventional treatment for coronary thrombosis while 589 received heparin or Dicumarol or both. Of those patients not receiving anticoagulant therapy, 23.4 per cent died as compared to a mortality of 16.0 per cent in the group receiving this form of treatment. It appeared from these findings that approximately one-third of the expected deaths was prevented by the administration of anticoagulant drugs. Similarly, when the percentage of cases developing thrombo-embolic complications was examined, it was found that in the control group 26.0 per cent developed one or more of these complications as compared with 10.9 per cent in the treated group. The greatest benefits in the reduction of mortality were in patients 60 years of age or over. The crude death rates for patients less than 60 years in both the treated and control

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groups did not show a significant difference but the incidence of thrombo-embolic complications was markedly lower in the treated group. Wright[19] has emphasized that even such nonfatal complications cannot be regarded lightly "since they leave some patients hopeless hemiplegics, others with a loss of one or more limbs by amputation or with similar serious disabilities." From these observations, the committee concluded that anticoagulants should be administered to every patient suffering from an acute coronary thrombosis unless definite contraindications are present.

Independent studies reported in medical literature throughout the world have, for the most part, confirmed the observations and conclusions of the American Heart Association's committee. The careful studies of Tulloch and Gilchrist[20] at the Royal Infirmary in Edinburgh, Scotland, in which seventy patients treated with anticoagulants were compared with eighty-four control subjects, led them to conclude that Dicumarol or related drugs reduced by one-half the mortality rate during the first six weeks after myocardial infarction. In their experience, thrombo-embolic complications also seemed similarly reduced and, when they did occur, fatalities were lessened. These conclusions, although derived from a relatively small series of cases, are based on careful and well-presented work in which the controls appear to fulfill most requirements. Some authors,[21,22] however, have pointed out the difficulties in collecting a series of untreated controls which are truly comparable to a treated series. The prognosis in acute myocardial infarction is influenced by many factors among which are age, sex, previous angina pectoris or infarction, shock, congestive heart failure, arrhythmias, and unrelated diseases. The difficulty in determining the prognosis after acute myocardial infarction is clearly indicated by reports presenting crude mortality rates varying from 8 to 78 per cent. Some[22] have lucidly presented the pitfalls in attempting to interpret such an apparently sound fact as mortality rate. It is well known that the death rate in any series of hospital cases is markedly influenced by the number of admissions within the first twenty-four hours of the attack. The series reported by Yater and associates,[23-25] for example, showed a mortality rate of 50 per cent in 866 male patients under 40 years of age. More than one-half of the fatal cases died within two hours of the attack. If all the immediate survivors had been sent to the hospital, the mortality rate calculated by the hospital staff could not have exceeded 30 per cent. Moreover, 18 per cent of the surviving group would have died within twenty-four hours and only 12 per cent thereafter, during the period of the acute illness. This simple analysis demonstrates that crude mortality figures mean little unless details are known. It indicates the difficulty in obtaining sufficiently well-controlled case material to evaluate the effect on mortality of any form of treatment in this disease. Immediate admission to the hospital was almost certainly uncommon in the series of Wright and his associates. Otherwise, the mortality rate in the first week would have been appreciably higher than in the second, whereas they were practically the same. It is possible that the figures presented by Wright and his group would have been even more impressive if a greater proportion of their patients had been seen and treated on the first day of their attack.

A few observers have reported no significant difference in mortality between patients who received Dicumarol and those who did not. In most instances, the reported series were relatively small and the accuracy of control undetermined. Some authors believe that the rather impressive favorable statistics recorded in the literature may have been due to effective suggestive therapy which accompanied the medical attention given to all patients receiving anticoagulant drugs. One critical observer[26] has commented that control subjects in such studies are often almost completely neglected even to the point of being deprived of essential nursing care. The statistical data concerned with the incidence of thrombo-embolic complications in the series of Wright and his associates have also been objects of critical analysis. The authors reported the incidence of thrombo-embolic complications in their control group to be 25.0 per cent, a figure in sharp contrast with the incidence of 11.5 per cent reported in the literature by others.[27] In recent years, however, a much higher clinical incidence for thrombo-embolic phenomena after coronary occlusion has been recorded, suggesting that in earlier reports minor episodes had been overlooked.

In spite of these "disturbing features" there appears to be ample evidence that anticoagulant therapy merits an important place in the management of acute myocardial infarction. Even if available statistics are not entirely acceptable as presented, they certainly cannot be disregarded. It is reasonable, however, to demand substantial evidence, for anticoagulant therapy is both a costly and troublesome procedure. Moreover, there are the dangers inherent in any interference with blood clotting: bleeding into the tissues generally, into the wall of the atheromatous coronary artery, and into the cardiac infarct itself. These considerations would be of no practical significance, however, if it could be shown from adequate and sufficiently controlled clinical material that anticoagulants have a beneficial effect in all cases of acute myocardial infarction.

In the light of present evidence, it is by no means certain that anticoagulant drugs should be used as a routine for all cases with this disease. Many physicians in general practice as well as specialists in internal medicine or cardiovascular disease do feel obliged to use an anticoagulant drug in every patient who sustains an attack of acute myocardial infarction. In some instances, this attitude is doubtless based on a firm personal conviction regarding the value of this form of treatment. In others, it takes origin from the authoritative pronouncement of the American Heart Association's committee that all cases should be treated in this manner. Many physicians who remain unconvinced or uncertain regarding the benefits to be derived from anticoagulant drugs continue their routine use chiefly because of fear of criticism by colleagues or of reproach by patients or their relatives who have been enlightened by medical articles in the lay press. Some physicians have candidly expressed real apprehension at the thought of possible litigation for malpractice if death or complications were to develop in their patients not receiving these drugs.

In order to justify the use of anticoagulants in all patients with acute myocardial infarction, it must be proved that, even in seemingly benign instances of the disease, the preventable mortality and morbidity significantly exceeds the incidence of complications and death attributable to the drug itself. Obviously,

if the benefit to be derived from Dicumarol in selected patients is found to be negligible when weighed against the hazards of hemorrhage inherent in this form of treatment, the needless expenditure of "time, trouble, and money" required to carry out this therapy would indeed be a wasteful extravagance. It is important, therefore, to determine whether the anticoagulant, like any other drug, may be indicated only under certain well-defined circumstances.

In previous studies[28,29] we have found that there is a strikingly low mortality rate and incidence of thrombo-embolism in selected "good risk" cases of acute myocardial infarction which are treated by conservative methods, exclusive of anticoagulant drugs. In order to study the natural course of the disease in such cases without specific treatment, we separated those which showed one or more of the following serious prognostic signs: (1) previous myocardial infarction, (2) intractable pain, (3) extreme degree or persistence of shock, (4) significant enlargement of the heart, (5) gallop rhythm, (6) congestive heart failure, (7) auricular fibrillation or flutter, ventricular tachycardia, or intraventricular block, and (8) diabetic acidosis, marked obesity, previous pulmonary embolism, varicosities in the lower extremities, thrombophlebitis (past or present), or other states predisposing to thrombosis. The patients who showed none of these criteria on

TABLE I. MORTALITY RATE AND INCIDENCE OF THROMBO-EMBOLIC COMPLICATIONS

	NO. OF CASES	MORTALITY		EMBOLIZATION	
		NO.	%	NO.	%
Total	1047	350	33.4	63	6.0
Good risk	489	15	3.1	4	0.8
Poor risk	558	335	60.0	59	10.6

the first day of hospitalization were classified as "good risks" to distinguish them from the "poor risk" group comprising those who manifested one or more of these unfavorable prognostic signs. An analysis was made of 1,047 consecutive admissions for acute myocardial infarction at the Maimonides and Kings County Hospitals in Brooklyn and the United States Public Health Service Hospital in Staten Island. Approximately 60 per cent of the total group of patients were admitted on the day of their attack. All of the cases were treated by conservative means without the use of anticoagulants. In the classification of patients into good risk and poor risk groups, only the facts in the history and physical examination which were available on the first day of admission to the hospital were considered. After such classification was completed, a study was made of the clinical course and subsequent outcome in each case. Our analysis showed that the mortality rate for the 1,047 cases in our series during the period of hospitalization was 33.4 per cent. When the patients were classified according to the clinical findings on the day of admission to the hospital, however, it was found that the mortality rate in the good risk group was only 3.1 per cent as compared to 60.0 per cent in the poor risk group. Similarly, the incidence of thrombo-embolic complications was 6.0 per cent in the total group, 10.6 per cent in the poor risk group, and only 0.8 per cent in the good risk group (Table I).

These results show that, in the clinical material provided by the patients who gained admission to our hospitals, there was a strikingly low mortality rate and incidence of thrombo-embolism among those who qualified as good risks when first seen on the day of entrance. With a mortality rate of only 3.1 per cent and an incidence of thrombo-embolism of 0.8 per cent, one appears justified in questioning the possible benefit which could be derived from the use of Dicumarol in such selected cases.

In attempting to determine the possible theoretical benefit which might have been achieved with the use of this drug in our 489 good risk patients, an analysis was undertaken of the causes of death in this group (Table II). Of the fifteen fatalities in the 489 good risk cases, seven occurred within forty-eight hours of admission to the hospital, and it is therefore unlikely that these deaths could have been prevented by Dicumarol. Two patients died from causes unrelated to their cardiovascular disease (one from peptic ulcer and one from septicemia and bronchopneumonia). One patient died from rupture of the left ventricle, and at autopsy there was no evidence that thrombo-embolism played any part in this termination. These ten deaths, therefore, could not have been prevented by Dicumarol. One patient died from a cerebral embolus and the remaining four patients died from causes not definitely known because autopsy was not obtained.

TABLE II. ANALYSIS OF CAUSES OF DEATH AMONG GOOD RISK PATIENTS

15 FATALITIES IN 489 CASES

CAUSES	NO. OF CASES
Within 48 hours	7
Unrelated causes	2
Rupture left ventricle	1
Cerebral embolus	1
Unknown	4
Total	15

If it is assumed that the latter five deaths could have been prevented under Dicumarol therapy (an assumption lacking confirmatory evidence), the theoretically preventable mortality in our good risk group would have been five out of 489 or 1.0 per cent. Consequently, no more than one death among every hundred patients in our series who sustained a mild attack could have been prevented if the prophylactic effect of Dicumarol were infallible. Moreover, if the drug worked to perfection it could avert only eight clinical thrombo-embolic episodes in every thousand patients since this was the total incidence of the complication in our good risk group. Even if minor episodes had been overlooked, such small theoretical benefit is certainly unimpressive when balanced against the risks inherent in any interference with blood clotting.

Increasing numbers of case reports are appearing in the literature in which hemorrhagic complications and death have resulted from the use of anticoagulants. Sporadic reports of single cases or groups of cases give no assistance in determining the relative frequency of deaths due to Dicumarol but they do indicate that such results can be encountered by physicians experienced in anticoagulant therapy. The data collected by Nichol[30] summarizing the experience of 136 physicians showed that major bleeding occurred in 2 per cent of approximately 15,500 anticoagulant-treated patients. In Nichol's own experience, the incidence of serious hemorrhage was 10 per cent. The mortality rate in his collected group from hemorrhage induced by heparin or Dicumarol was 0.18 per cent. Most of the available statistics concerned with the dangers of anticoagulant therapy, however, reflect the experience of skilled investigators in large medical centers where excellent facilities for prothrombin determinations exist. Consideration should be given to the probable results of therapy administered in smaller hospitals or in the patient's home under the guidance of less skilled hands. It must not be overlooked that general practitioners treat the vast majority of patients with acute myocardial infarction. Moreover, it is in the milder cases that the general practitioner is likely to have exclusive control without benefit of consultation.

Wright and his associates[16,18,19] observed no improvement in death rate in unselected Dicumarolized patients under 60 years. Obviously, if this therapy does not influence the death rate in groups in which thrombo-embolism is said to be prevalent, it should not be expected to serve any useful purpose and, in fact, may be detrimental in selected good risk cases in which, as we have shown, the incidence of thrombo-embolism is strikingly low. The observation that Dicumarol improved the mortality rate only in older patients warrants careful analysis. Wright's interpretation of this finding is that "younger people survive thrombo-embolic complications more readily than older people even though they have as many or more." This concept, however, lacks confirmation since other workers have found that the improvement in prognosis by anticoagulant therapy is independent of age. The failure to demonstrate a reduction in mortality among Dicumarolized patients under 60 years of age could more logically be explained by the fact that relatively few of the patients in the series of Wright and co-workers were admitted to the hospital on the day of their attack so that the institution of therapy was unavoidably delayed in most instances. Moreover, the low mortality rate of 10 per cent which was reported for the control group under the age of 60 years would seem to suggest that the control sample at least contained relatively few instances of serious attacks. For a similar group of patients, Tulloch and Gilchrist[20] reported a mortality rate of 29.0 per cent and our own studies[29] showed the frequency of death to be almost identical (28.8 per cent). Consequently, either the control series of Wright and associates may not have been comparable to their treated series in the younger age group or, if it was, the relative paucity of serious cases may not have permitted anticoagulants to be statistically life saving.

Our findings[31] are not in accord with the view which assumes that age, per se, is a determinant of the individual patient's ability to survive an acute attack of

TABLE III. ANALYSIS OF 1047 CASES OF ACUTE MYOCARDIAL INFARCTION ACCORDING TO AGE AND SEVERITY OF ATTACK

AGE OF PATIENTS	TOTAL	GOOD RISK		POOR RISK	
		NO.	%	NO.	%
All ages	1047	489	46.7	558	53.3
Under 60 years	618	331	53.6	287	46.4
60 years or over	429	158	36.8	271	63.2

myocardial infarction. It is true that crude statistics show that the mortality rate from this disease increases with advancing years but such statistical differences could be due simply to a higher incidence of severe attacks in later life rather than to a specific influence of age on survival in the individual case. No evidence has been produced to date to justify the common belief that a patient over the age of 60 years has a greater risk of dying from acute myocardial infarction than a younger patient who has sustained an attack of similar severity. Previous mortality studies have not been corrected for differences in the severity of attacks, the clinical signs, or the incidence of previous myocardial damage. Obviously, similar cases must be compared in different age groups if a true concept is to be formulated regarding the elderly patient's relative capacity for survival. Our studies actually demonstrate that the elderly good risk patient or poor risk patient has no worse a chance for survival than the younger patient with similar clinical findings. It can be seen from Table III that less than one-half of the patients under the age of 60 years were poor risk cases whereas almost two-thirds

TABLE IV. MORTALITY RATE IN 1047 CASES OF ACUTE MYOCARDIAL INFARCTION ACCORDING TO AGE AND SEVERITY OF ATTACK

AGES OF PATIENTS	TOTAL (%)	GOOD RISK (%)	POOR RISK (%)
All ages	33.4	3.1	60.0
Under 60 years	28.8	3.0	58.5
60 years or over	40.1	3.2	61.6

of those 60 years of age or older belonged to the same category. When the mortality rates were calculated on the basis of age and the severity of the attack, it was found that age had no influence on prognosis (Table IV). The good risk patients of either age group had a strikingly similar death rate (3.0 per cent as compared with 3.2 per cent). Similar findings were noted from comparison of the poor risk groups (58.5 per cent as compared with 61.6 per cent). It can be seen that this important information had heretofore been buried in the over-all statistics reflecting age group prognosis. The higher mortality rate recorded for old age groups is therefore merely a statistical phenomenon of interest to the actuary but of little real significance to the practicing physician.

Our observations seem to indicate that the history and the clinical signs and symptoms in any given case and not the age of the patient provide the data necessary for prognosis and for decision with regard to the use of anticoagulant drugs. Any increased benefit recorded from anticoagulant therapy in older age groups would therefore appear to depend on the higher incidence of serious attacks in older people and the correspondingly higher incidence of thrombo-embolism. The good risk elderly patient is no more in need of anticoagulants than the good risk younger patient. It would seem, therefore, that the small benefit to be derived from Dicumarol in good risk patients of any age is more than likely to be nullified or even overbalanced by complications induced by this drug. In the milder cases, the employment of such measures as the low bed, bedside commode, early armchair treatment, and mild active and passive exercise to encourage circulation in the extremities would very likely leave little room for even theoretical benefit from the use of anticoagulant drugs. In our opinion they should be reserved for the more serious cases of acute myocardial infarction in which the frequency of thrombo-embolism justifies the risk entailed in their use.

In order to determine the current opinions of leading internists and cardiologists concerning the use of anticoagulant drugs in acute myocardial infarction, a questionnaire was forwarded to a large number of such specialists in various medical centers throughout the United States. On the basis of 228 replies received in this manner, a cross section of authoritative opinion was obtained which may be summarized as follows:

1. More than one-half (50.9 per cent) of the 228 physicians interrogated in this survey do not employ anticoagulants as a routine measure in the treatment of acute myocardial infarction. Even when no contraindications exist, 111 of these specialists are guided entirely by the history and the severity of the clinical signs and symptoms in the individual case. Five physicians do not use anticoagulant therapy at all, since they strongly doubt that its value outweighs its potential hazards.

2. The 111 physicians advocating selection of cases on the basis of clinical findings enumerated the following criteria as indications for anticoagulant therapy: previous myocardial infarction, the presence of a large infarct, profound or persistent shock, intractable pain, significant enlargement of the heart, cardiac arrhythmias, thrombo-embolic phenomena, varicosities, previous or recent thrombophlebitis or phlebothrombosis, old age, debility, lethargy, obesity, diabetes, polycythemia, and any other departure from a smooth or uneventful course.

3. Most physicians in the former group regard old age as an important indication for the use of anticoagulants but several of them consider it to be a distinct contraindication. The fallacy in regarding age as a significant factor in prognosis in the individual case has already been emphasized by the authors.

4. There were 112, or 49.1 per cent, of the 228 physicians in the total series who reported that they routinely employ anticoagulants in all cases of acute myocardial infarction when no contraindications exist. A small number of this group emphasized that they have actually been forced to follow this practice since failure to use these drugs "is often construed by the family, referring physician, and consultant as mistreatment."

5. There was unanimity of opinion regarding the necessity for hospitalization and dependable laboratory facilities in every case of acute myocardial infarction in which anticoagulants are to be employed.

6. Among nonmedical factors influencing the decision to employ or withhold anticoagulant drugs were: (a) economic status of the patient, (b) coercion by the patient's family or referring physician, (c) the compelling influence of the wide publicity given to this form of treatment, and (d) fear of criticism or litigation for malpractice if such treatment were withheld.

7. Most physicians who replied to the questionnaire either use Dicumarol alone or in combination with heparin. More than one-half of those who employ heparin reserve it exclusively for the more serious cases. Only 31.6 per cent of the total of 228 physicians invariably prescribe this drug when ordering Dicumarol. Tromexan is being used alone or in conjunction with Dicumarol and/or heparin by a smaller but significant number of the physicians contacted in this study.

8. Serious hemorrhagic complications resulting from anticoagulant therapy were encountered by 104, or 45.6 per cent, of the 228 physicians in this study. One hundred and twenty-two deaths caused by such complications were reported by 64, or 28.1 per cent, of the total group. The brain, gastrointestinal tract, and pericardium in this order were found to be the commonest sites of fatal hemorrhage. Individual reports of the incidence of major hemorrhage based on personal observations varied from 0.25 per cent, with no deaths from this complication, to 10.0 per cent, with four fatalities due to hemorrhage in 100 anticoagulant-treated patients.

From the foregoing, it is concluded that neither the evidence to date nor the current method of usage by authorities in the field can support the concept that the routine employment of anticoagulant therapy in acute myocardial infarction is necessary or desirable.

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A QUANTITATIVE STETHOSCOPE AND ITS CLINICAL APPLICATIONS

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DIFFERENCES in the loudness of the heart sounds and murmurs have long been used in the diagnosis of heart disease. In the case of the heart sounds, these differences were determined by comparing the first with the second heart sound at the same location of the stethoscope, or by comparing the same heart sounds at different regions,[1] but no attempt was made to make a quantitative appraisal of their intensity. In the case of cardiac murmurs, a very useful loudness scale was set up by Levine,[2] but this scale was purely subjective, and several weeks of training under the guidance of its originator were held to be necessary to learn its exact application. In the present paper, a simple stethoscope is described which makes it possible to measure the loudness of the cardiac sounds and murmurs directly in decibels above normal hearing threshold; this makes it also possible to assign objective values to Levine's scale. At the same time, a discussion of the factors will be given which would have to be taken into consideration for a correct evaluation of the intensities as measured in this way.

The principle of the quantitative stethoscope described in this paper is to reduce progressively the area of the opening between the bell of a stethoscope and the tube leading to the earpieces until a certain sound or murmur can no longer be heard, that is, until the intensity of the sound reaching the ear is below the hearing threshold of the person listening to it. If it has previously been found that a calibrating sound of a given intensity and comparable frequency, originating in the bell of the stethoscope, is just on the threshold of hearing when the opening is of this area, then the intensity of the heart sound or murmur is equal to that of the calibrating sound. For clinical purposes it is important to compare the subjective loudness of the sounds as they are rather than the absolute intensities of the vibrations. The most convenient unit of loudness, as used in audiometry, is the decibel, which corresponds to an increase of 1:2 times in the intensity of vibration; an increase of 20 decibels corresponds to a tenfold increase of the intensity.[5,6] The loudness of the heart sounds and murmurs is therefore best expressed in decibels above the normal hearing threshold. As the vibration intensity in the earpiece of a stethoscope is approximately proportional to the area of the aperture between the bell and this earpiece, as long as this area is small, logarithmic changes in this area should cause linear changes in the loudness of the sound reaching the ear (Weber-Fechner's law).

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The author's quantitative stethoscope[3] (Fig. 1) uses a standard size Bowles bell with a semirigid membrane. The choice of this bell was prompted by the fact that it shows much less variation in the intensity of the transmitted sounds with varying pressure against the chest wall than the open bell type.[4,5] Furthermore, it is used by a greater number of physicians for cardiac auscultation. The metal tube bearing the rubber connections to the earpieces is partially occluded by the rim of a metal cylinder (Fig. 2) in such a way that rotating the cylinder counterclockwise equal numbers of degrees causes an approximately logarithmic

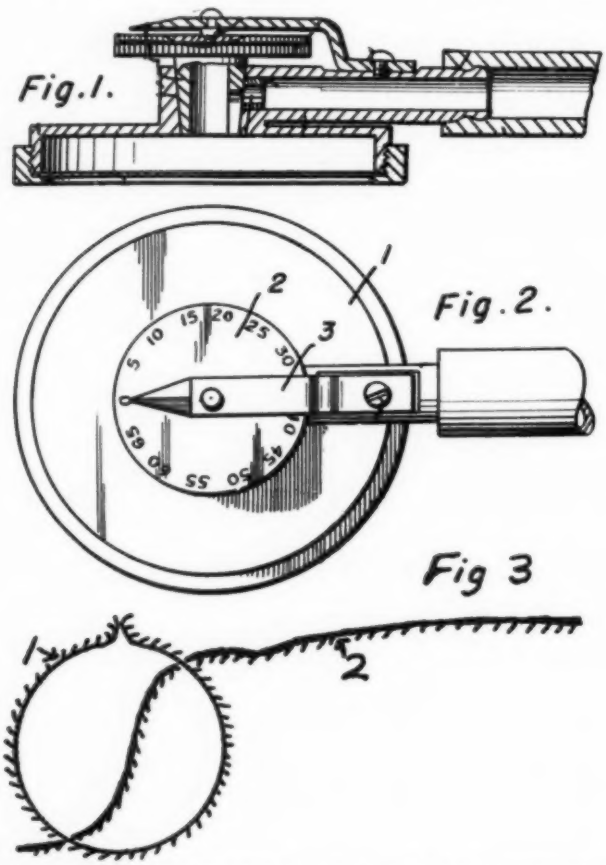

Fig. 1.—Cross section through the calibrated stethoscope. For explanation see text.
Fig. 2.—Top view of the calibrated stethoscope. *1*, Stethoscope bell; *2*, dial; *3*, pointer and spring.
Fig. 3.—Magnified aperture (*1*) and edge of cylinder (*2*), in cylindrical projection. The relative position of these parts as pictured corresponds to an attenuation of about −5 decibels.

decrease in the area of the opening. To make possible a finer adjustment in the range of small areas, the opening of the side tube is not circular, but approximately pyriform in shape, having a tapering projection on one side (Fig. 3). The projection of the occluding metal cylinder is approximately helicoid in shape (Fig. 3). Its exact shape must be determined empirically during the calibration of each master model, by filing away the edge with a rotary bur for each position of the dial until the correct attenuation is obtained. To designate each position of the

cylinder, the knurled knob by means of which the cylinder is rotated bears a dial on its upper surface; an extension of the spring which holds the cylinder in place acts as a pointer.

The *calibration* of the master model was carried out with the help of a Maico Audiometer. For this purpose the stethoscope bell, with its membrane removed, was pressed firmly to the sponge-rubber cushion of the audiometer earpiece; the vibrating membrane of the earphone in the latter then corresponds to the membrane ordinarily covering the stethoscope bell. As the most important pathologic murmurs have a frequency of around 250 cycles per second (see later), a tone having this frequency was used for calibration. After it was determined that the calibrating person had a normal hearing threshold for this frequency, the dial of the stethoscope was subdivided into twelve equal parts of about 15 degrees each, to indicate degrees of attenuation from 0 to 60 decibels. At the position of 0, the edge of the obstructing cylinder was filed away with a rotary bur until it did not obstruct the opening at all. At the position of 5, it was filed away so that it obstructed the opening just enough to reduce a sound of 5 decibels above hearing threshold, originating in the audiometer, to threshold loudness. At the position of 10, it was filed away just enough to reduce a sound of 10 decibels to threshold value. This procedure was repeated until all the positions up to 60 decibels have been calibrated. It has not been possible to obtain an attenuation much above 60 decibels, as sounds having this loudness above threshold can be heard even with the opening completely closed, being transmitted along the metal parts of the stethoscope. Once the master model has been made, copies of this model can be reproduced by casting them in plastic or alloys.

The calibrating frequency of 256 cycles per second was chosen because this corresponded most closely to the mean frequency of the cardiac murmurs.[7-10] However, the heart sounds have a lower mean frequency, while the frequencies contained in the heart murmurs may reach 1000 cycles per second[7-11] or even 4000 cycles per second.[12,11] The attenuation of the different frequencies within this range at each position of the stethoscope dial was therefore studied. In Table I it is expressed in decibels above or below the degree of attenuation for the calibrating frequency.

It can be seen from Table I that as the area of the opening is decreased and the degree of attenuation increases, the lower pitched sounds appear louder than the higher pitched sounds of the same original intensity. The reason for this is that when the period of vibration is small, the amount of air forced through the opening is no longer sufficient to produce a full increment of pressure inside the tubes. The greatest difference is apparently between 256 and 512 cycles per second. The fall in intensity beyond 1024 cycles per second found at some positions may be due to resonance phenomena; these become very marked at high frequencies. The stethoscope measures the intensity of the loudest frequency components, which usually lie below 400 cycles per second, where the frequency plays only a minor role in the loudness determinations, so that the differences of attenuation described in Table I would probably be of only small practical significance.

Adjustment for Individual Hearing Acuity.—As mentioned above, the stethoscope is calibrated for the average hearing threshold. In case the person desiring to use the stethoscope shows considerable deviation from the normal in his hearing acuity, the screw at the center of the index plate is loosened and the plate rotated so that the notch on the knurled knob underneath the plate is situated opposite the number corresponding to the loss of hearing in decibels at the frequency of 256 cycles per second. For normal hearing acuity, this notch corresponds to the 0 mark on the index plate. The degree of hearing loss must be determined in each case by means of an audiometer at the office of an otolaryngologist.

TABLE I. DIFFERENCES IN INTENSITY (IN DECIBELS) OF DIFFERENT FREQUENCIES AT EACH POSITION OF THE STETHOSCOPE DIAL, AS COMPARED TO THE INTENSITY OF THE CALIBRATING FREQUENCY (256 CYCLES PER SECOND)

POSITION OF DIAL	FREQUENCY (CYCLES PER SECOND)							
	64	128	256	512	1024	2048	2896	4096
0 with membrane	−5	−5	0	0	0	−5	0	0
0 without membrane	0	0	0	0	0	0	0	0
10 without membrane	+5	0	0	−5	−5	−5	−5	−5
20 without membrane	+10	+5	0	−5	−5	−5	−5	−5
30 without membrane	+10	+5	0	−10	−10	−10	−5	−5
40 without membrane	+5	+5	0	−15	−15	−10	−10	−15
50 without membrane	+5	+5	0	−20	−20	−20	−20	−20
60 without membrane	+5	+5	0	−25	−25	−25	−25	−25

A simple method of calibration, which takes into consideration the actual hearing acuity at the time of auscultation, makes use of the friction sound produced by dragging slowly a strip of crepe tissue paper across the most sensitive central part of the stethoscope membrane, held in horizontal position. For the paper used by the author, this sound was always between 15 and 20, on the average 18 decibels above hearing threshold; that is, it was just audible when the dial was in this position. The strip must be cut perpendicular to the direction of the crepe creases, which makes it pliable enough for each section of the strip to press down on the membrane only with its own weight. Such a strip, enclosed in a small protective folder, can be carried at all times on the frame of the stethoscope. If the friction sound can be heard only at a lower position of the dial, the difference between 18 and this number must be added to the results of all measurements performed at this particular time.

After the correct position of the index plate, or the proper correction number, has been determined in this way, the actual *determination* of the intensity of a certain auscultatory sound is made as follows: The knob of the stethoscope is first set at the 0 position and the different heart sounds and murmurs identified. Then the knob is turned slowly in a counterclockwise direction until the particular sound or murmur whose intensity is the object of study is no longer heard; the number opposite the pointer on the dial then corresponds to the loudness of the murmur in decibels above average hearing threshold. The procedure may be repeated several times, and the average of the readings taken. In order to mini-

mize the sources of error inherent in such a determination, the factors described below must be taken into consideration. They are enumerated in order of their location from the ear to the heart.

Spontaneous Variations of the Hearing Acuity.—It is well known that the hearing threshold rises greatly during any acute pathologic involvement of the inner or middle ear. Even a slight head cold can raise it considerably, due to obstruction of the Eustachian tube. On the other hand, gradual accumulation of cerumen in the external auditory passage may cause a noticeable increase of this threshold. The physiologic decrease of hearing acuity in old age concerns above all the frequency range above 5000, which does not seem to appear in auscultatory phenomena. Every during the course of the day there are normal variations of hearing acuity. These become marked in the case of fatigue, or after the ear has been subject to noises of high intensity. In all such cases, the hearing threshold should be determined, especially if one of the conditions which raises it is known to exist. A test of sufficient exactitude is the calibration by means of the friction sound, as described above; this can be conveniently carried out before each set of measurements.

Masking of Sounds.—It is well known that the hearing threshold for a certain sound is elevated when another sound is present at the same time. It is clear, accordingly, that the room where the measurement is being carried out should be completely quiet and that breath sounds should be avoided by making the patient hold his breath during measurement. Sounds due to rubbing of the stethoscope tubes against skin, clothing, or against each other, are easily avoided. More difficult is the suppression of the sound due to muscular tremor of the hand which holds the stethoscope bell against the patient. This can usually be minimized by resting the ball of the hand on the patient's chest and by grasping the knob very lightly. An important source of interfering sound is the tetanic contraction of the masseters, which persists as long as the mouth is kept closed. This sound can be eliminated by letting the jaw hang loosely during measurement. This may give the physician a dumbfounded expression, but is indispensable for accurate measurement of threshold sounds. In fact, the expression "open-mouthed attention" may have originated from this fact.

The masking effect of strong sounds may persist for several tenths of a second after termination of the sound; part of this may be due to reflex contraction of the tensor tympani muscle. In this way, a loud first heart sound may mask a protosystolic murmur or a loud second sound mask a protodiastolic murmur. There is no remedy for this situation at present.

Varying Pressure of the Bell Membrane against the skin causes the amount of sound transmitted by the skin and membrane to vary. Increasing this pressure causes increased damping of the membrane and decreases the intensity of the transmitted sound, especially in the lower frequency ranges.[4,5] These effects are much smaller when a stiff membrane is used than in an open-bell stethoscope, where the skin itself acts as a membrane. However, they are still an important source of error, and should be kept as small as possible by applying only just enough pressure to the bell to prevent it from slipping when the knob is turned.

The presence of hair between the skin and membrane can interfere with sound conduction considerably by creating a poorly conducting layer of air between skin and membrane. To prevent this, the air spaces between the hairs should be filled by applying water or electrode paste to the site of auscultation, or the hair should be shaved. An even greater source of error is introduced in very lean persons where projecting ribs may make it impossible to attain complete contact between the stethoscope membrane and the skin throughout the entire area of the bell. In this case it is better to have one rib contact the more sensitive central portion of the membrane than two ribs contact the less sensitive peripheral regions.

Changes in the Conductivity of the Thoracic Tissues between the heart or great arteries and the chest surface are a major source of error. Lung tissue has a far smaller conductivity than any other tissue. It is well known that in pulmonary emphysema the heart sounds and murmurs may become very muffled. During respiration the amount of lung tissue between the heart and the stethoscope also changes. To minimize this latter factor, the measurement of intensity should be always made in the same position and at the same phase of respiration, preferably in the pause between two respirations, in natural expiratory position. One method to measure the sound conduction to the stethoscope would be to introduce a small loud-speaker producing sound of known intensity into the esophagus and to measure the loudness of this sound at each place of auscultation. A simpler method has been tried by the author in a limited number of cases. It consists of placing an alarm clock on a pillow and having the patient lie down on the clock; when the alarm is set off, the intensity of the buzzer sound in each region used for auscultation is measured. However, the sound in this case does not originate in the heart or even in the mediastinum. A third possibility would be to measure the distance of the heart from the chest wall roentgenologically, and to correlate this distance with the results of the auscultatory measurements. However, these measurements will still be of value clinically even without such a correlation.

After the factors mentioned in the preceding paragraphs have been taken into consideration, the measurements of the intensity of cardiac sounds and murmurs can be interpreted in the light of purely clinical experience. So, for instance, it has been found by using the stethoscope that Levine's classification of cardiac murmurs into six grades corresponds approximately to differences in loudness of 10 decibels per grade, from 10 to 60.[14] Levine's findings that grade three is approximately the border line between the "accidental" and the organic systolic murmurs[2] could be confirmed. However, in order to gain a deeper insight into the mechanism and significance of these findings, and to improve the diagnostic correlations, a number of additional factors can be studied. The intensity of murmurs produced by the blood stream depends on three main factors: the configuration of the blood vessel or cardiac chamber, the velocity of blood flow, and the blood viscosity, independently of the blood velocity.[15] Of these, only the first factor is of clinical interest, as it is of value in the differentiation of the functional from the organic murmurs. This differentiation would

therefore be enhanced by correlating the intensity of the murmur to the other two factors. The blood viscosity can be measured directly, but as it depends largely on the relative volume of the red blood corpuscles,[15] a correlation to the hematocrit value or even the red blood count, which is usually determined routinely, would be of sufficient exactitude. The blood velocity in the case of the systolic murmurs, ceteris paribus, varies inversely with the heart rate, as at low heart rates the systolic interval forms a smaller percentage of the total heart cycle, causing a given heart output to be concentrated in a shorter interval. This is why a systolic murmur in many cases is more intense at low heart rates.[2] However, when the increase of heart rate is accompanied by increase of the heart output, as after exercise, the systolic blood velocity actually increases and systolic murmurs usually become accentuated.[2] There is at present no simple method of determining the systolic aortic velocity, but the ballistocardiogram can furnish information about the rate of systolic acceleration of the aortic blood. A study is now in progress to correlate the amplitude of the ballistocardiographic deflections with the intensity of systolic murmurs.

The intensity of the first heart sound is of clinical importance in the diagnosis of mitral stenosis, where it is elevated, and in some cases of myocardial failure or fibrosis, where it is depressed. In the first case, the mitral valve is kept open at the time of the next ventricular contraction by increased left auricular pressure, causing a longer path of movement and a more intense closure of the mitral valves. The increased stiffness of the valves also contributes to the loudness of the sound caused by their closure. As the valves are forced apart by the blood stream entering during auricular contraction, the intensity of the first heart sound depends on the interval between auricular and ventricular contraction, or on the P-R interval.[2] In order to obtain more exact results, it would be accordingly of value to correlate the actually measured loudness with the P-R interval and with the heart rate.

Another important measurement is the loudness of the second heart sound over the pulmonary area, which can be an indication of pulmonary hypertension. Usually, the intensity of this sound is compared with that of the second sound over the aortic area, but if the second aortic sound is also accentuated due to the presence of hypertension or aortic sclerosis, this comparison will not yield satisfactory results. In this case, the absolute measurement of the intensity would give more exact information.

SUMMARY

A simple stethoscope is described. It allows the measurement of the intensity of cardiac sounds and murmurs in decibels above the normal hearing threshold. The size of the instrument does not exceed that of the conventional stethoscope. The acoustic characteristics of the stethoscope and methods of minimizing sources of error during measurement are described. The practical value of the stethoscope lies in the possibility of quantitative measurement of the loudness of the heart murmurs and sounds (especially that of the systolic murmurs and of the first heart sound), which in turn may give aid in the differentiation between

functional and organic murmurs and in the early recognition of valvular heart disease. To facilitate this differentiation, further correlations to the conductivity for sound of the thorax, the heart rate, and blood velocity as well as the P-R interval of the electrocardiogram are proposed.

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Clinical Reports

GANGRENE RESULTING FROM THROMBOARTERITIS, APPARENTLY OF RHEUMATIC FEVER ORIGIN

With Special Reference to Histopathology of Rheumatic Aortitis and Arteritis and Occurrence of Thrombosis

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NO REFERENCE can be found in the medical literature as to the occurrence of gangrene in rheumatic fever. In the following case, which came to autopsy, gangrene of the right foot and leg had been the chief complaint of the patient during life and was found post mortem to be caused by thromboarteritis of the iliac and femoral arteries, apparently of rheumatic fever origin. The rarity of such an occurrence warrants reporting. It is also proposed to review the histopathology of rheumatic aortitis and arteritis, to compare it with what was observed in the present case, and to ascertain the incidence of thrombosis in rheumatic fever.

CASE REPORT

Kao, a 21-year-old housewife, native of Tseng-Hua, Hopeh Province, was seen on March 14, 1947. The chief complaint was of gangrene of the right leg. Two months before admission, she began to have palpitation of the heart and dyspnea, associated with slight cough. One month before admission, pitting edema appeared on the face and in both lower extremities, being particularly marked in the right leg, which was also very painful. Twenty days before admission, she experienced a sensation of coldness of the skin of this leg. Six days before admission, the skin of the dorsum of the right foot began to change color, first from normal to pink, then to red-purple, and finally to black, with aggravation of the pain. The area of skin discoloration gradually enlarged until, at the time of admission, the entire right foot and leg were black and gangrenous. The patient did not remember any attack of sore throat, joint pain, palpitation of heart, or dyspnea in the past. The patient's mother had died of asthma.

Physical Examination.—The temperature was 38°C.; pulse rate, 124 beats per minute; respiration rate, 27 per minute, and blood pressure, 122/70 mm. Hg. The patient was drowsy, and the face pale. There was generalized edema; there were no jaundice, no subcutaneous nodules, and no adenopathy. The pupil reflexes, visual fields, and ears and nose were normal, while the neck veins were distended. There were wheezing râles heard over both lung fields and fine moist râles at both bases. The cardiac dullness was enlarged both to the right and left, and the apex impulse was present in the fifth intercostal space at the left anterior axillary line. A soft systolic

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murmur was heard at the apex with a gallop rhythm, and the P_2 was greater than the A_2. The abdomen was distended, with slight tenderness in the right hypochondrium, but no shifting dullness was detected. The liver was palpable 7.5 cm. below the right costal margin. The right lower extremity below the knee was cold and almost black in color. There was no pulse felt in the dorsalis pedis artery and the posterior tibial artery, but pulsations were present in the arteries above the knee.

Laboratory Examination.—The red blood count was 2.7 million; hemoglobin, 5.6 Gm; white blood count, 8,950. Urinalysis showed albumin 3 plus; white blood count, 2 to 4 per high-power field; hyaline casts, plus. Stool examination showed ascaris ova present. Blood Wassermann test was negative, blood nonprotein nitrogen, 49.3 mg., plasma protein, 5.88 Gm. Renal function was 45 per cent in 2 hours; blood culture, negative.

Clinical Course.—Patient was given, after admission, a total dose of 1.5 Gm. of digitalis folia in 3 days. This was not followed by improvement. The temperature fluctuated between 38°C. and 39°C. Slight leukocytosis (10,300) was noticed. Because the patient had excruciating pain, amputation of the right leg and foot was performed on March 17, followed by intramuscular penicillin injections. The leukocytes and temperature were normal on the next day; the gallop rhythm also disappeared and the blood pressure rose to 136/80 mm. Hg. Blood transfusion (150 c.c. whole blood) was given on the second day after operation. Edema of the left lower extremity improved but the urinary findings remained unchanged. The wound of the stump healed after skin grafting. On March 21, a low-grade fever reappeared and persisted between 37°C. and 38°C., with a pulse rate varying between 80 and 140 per minute. A decubitus ulcer appeared in the sacral region on March 26. On the same day, a second blood transfusion (150 c.c.) was given, followed by a rise of the red count to 3.4 million and hemoglobin to 7.9 Gm. A blowing systolic murmur was heard at the apex on March 29, together with a precordial friction rub which persisted to the day before death. There was, however, no increase in the area of cardiac dullness nor aggravation of the symptoms of cardiac decompensation. The blood nonprotein nitrogen was unchanged. Patient had marked drowsiness for a week before death on April 1.

Clinical Diagnosis.—Rheumatic heart disease; rheumatic myocarditis and pericarditis; heart failure; chronic passive congestion of liver and kidneys; thrombosis of right femoral artery and gangrene of right leg and foot; secondary anemia; ascariasis.

Autopsy.*—

Heart: The epicardial surface was grossly smooth. There was distinct dilatation and hypertrophy of all the cardiac chambers. No valvular lesion, either fresh or chronic, was present. The left ventricle showed a mural thrombus adherent to its endocardial surface. The cut surface of the left ventricle showed endocardial thickening and the presence of scars in the myocardium. The left auricle showed a partly organized and partly fresh mural thrombus. The right ventricle also showed myocardial scarring, endocardial thickening, and mural thrombosis. The right and left coronary arteries were normal.

Parietal pericardium: One surface showed a velvety appearance; the other surface was smooth.

Aorta: The specimen consisted of the lower portion of the abdominal aorta, including its bifurcation and the right iliac artery. Fresh mural thrombi were found adherent to aortic intimal surface. The iliac artery showed thickening of its walls and its lumen was occluded by a fresh thrombus.

Femoral artery (right): The specimen measured 5 cm. in length. It was obstructed by a greyish-white fresh thrombus which was continuous with a propagated red clot.

Spleen: The organ was enlarged and showed a small greyish-white infarct. The splenic pulp revealed a dark red color and a rather firm consistency.

Liver: A small block of liver tissue was received. It showed many red spots suggestive of nutmeg liver.

***The organs were removed from the body by Dr. C. M. Lin, Chief Surgeon of the First Municipal Hospital of Tientsin, and sent to the senior author for macroscopic and microscopic examination.**

Kidneys: Both were swollen and congested. The right kidney showed two small depressed areas (healed infarcts) in the cortical tissue. The left one showed many petechial spots in the cortex externally and on section.

Microscopic Examination.—

Parietal pericardium: The outer dense collagenous layer showed areas of fibrinoid degeneration of collagen (Fig. 1). The inner mesothelial (serous) surface was covered with a layer of

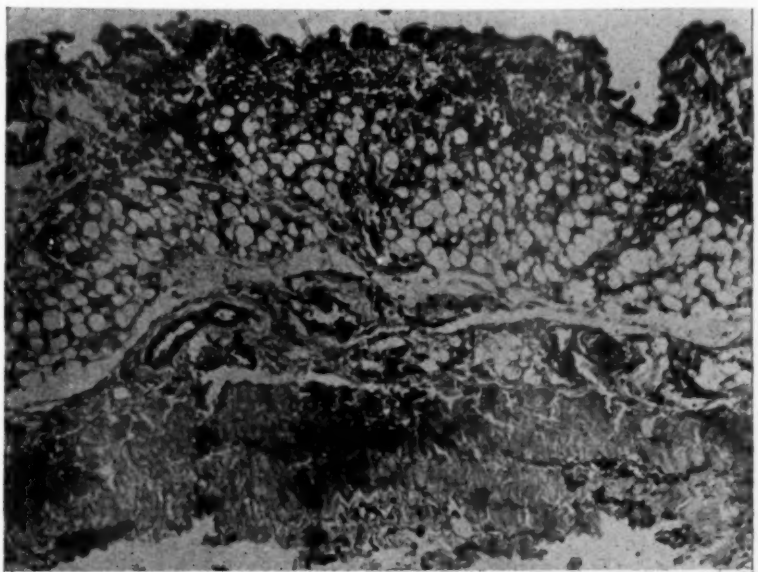

Fig. 1.

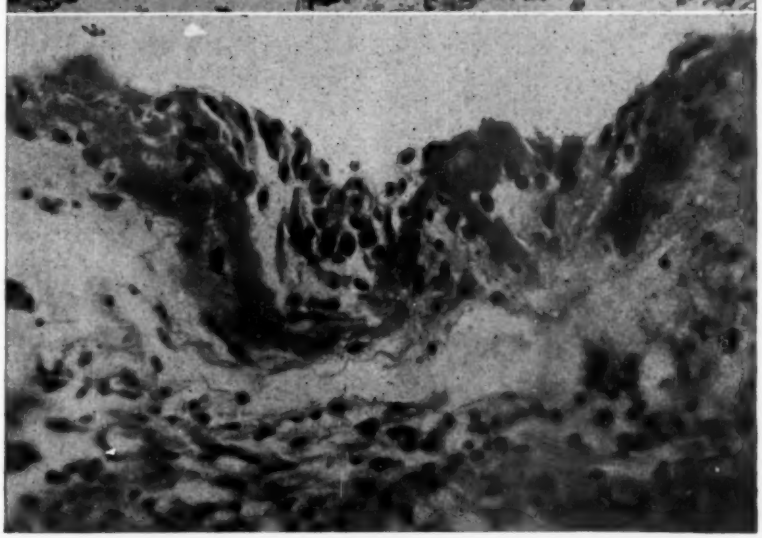

Fig. 2.

Fig. 1.—Parietal pericardium, with serous (mesothelial) surface above and dense collagenous layer below, showing fibrinous exudate on the serous surface, cellular infiltration of the subpericardial fibro-adipose tissue, and areas of fibrinoid degeneration (deeper eosinophilic staining) in the collagen layer. ×80.

Fig. 2.—Parietal pericardium, showing hyalinized fibrin (without leukocytes) on the inner (serous) surface with proliferation of fibroblasts and presence of Aschoff cells. The subpericardial fibrous tissue shows lymphocytic and plasma-cell infiltration and also fibroblastic proliferation. Fat cells are seen at the bottom. ×200.

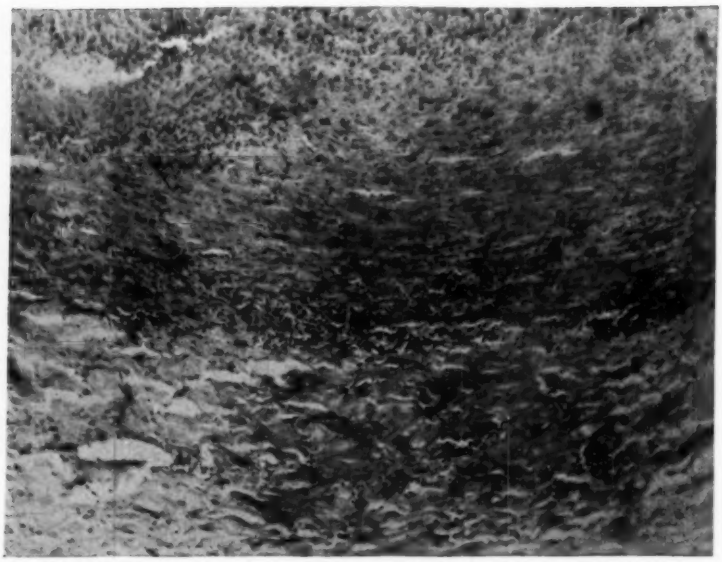

Fig. 3.—Wall of aorta with media in the center, intima (only partially shown) above, and adventitia (only partially shown) below, showing increase of vascularity and inflammatory-cell infiltration in the outer half of media, fibrinoid degeneration of the collagen and cellular infiltration of adventitia, and fibroblastic proliferation and cellular infiltration in the intima. ×80.

Fig. 4.—Wall of aorta with adventitia (complete thickness) above and the outer portion of media below, showing conspicuous perivascular lymphocytic infiltration and foci of fibrinoid degeneration of the collagen in the adventitia, and very dense lymphocytic infiltration of the outer portion of the media. ×80.

hyalinized fibrin with absence of polymorphonuclear leukocytes, while many typical Aschoff cells (proliferating connective tissue cells with plump basophilic cytoplasm and hypertrophic nuclei) were present (Fig. 2). The subpericardial fibroadipose tissue showed lymphocytic and plasma-cell infiltration (Fig. 1); in the fibrous tissue there was also proliferation of fibroblasts (Fig. 2).

Heart: 1. Right ventricle: A large mural thrombus, rather fresh, was intimately adherent to the endocardium which showed fibrotic thickening and infiltration with phagocytes, lymphocytes, and plasma cells. No Aschoff cells were seen. In the subjacent myocardium, there were patches of scar tissue infiltrated with similar cells and occasional leukocytes. The myocardium elsewhere showed hypertrophy of the cardiac fibers and a slight degree of interstitial fibrosis and round-cell infiltration. No Aschoff bodies were found.

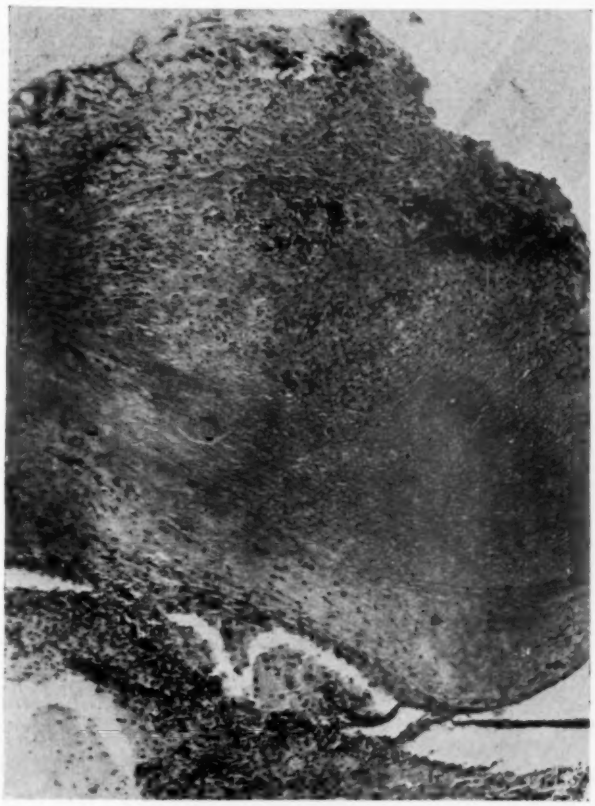

Fig. 5.—Wall of aorta with adventitia on the top and mural thrombus (attached to the intima) at the bottom. The adventitia shows thickening and cellular infiltration. The media shows focal lymphocytic infiltration, and areas of hyalin necrosis extending from the intima. The latter shows a nodular area of tremendous thickening which is almost totally affected with fibrinoid or hyalin necrosis. The necrotic area is surrounded by fibroblastic proliferation. The mural thrombus shows cellular infiltration and fibroblastic proliferation in its peripheral portion adjoining the intima. ×80.

2. Left ventricle: The mural endocardium was greatly altered by fibrosis and infiltrated with the same cells as seen in the right ventricular endocardium. A fresh mural thrombus was intimately attached to the thickened endocardium. In the myocardium, there were seen scars infiltrated with round cells, and a vein occluded by an organized thrombus. No Aschoff bodies were found.

3. Epicardium: The epicardium of both right and left ventricles showed round-cell infiltration but no fibrinous exudate.

4. Left auricle: The mural thrombus consisted of hyalinized fibrin such as is found in rheumatic valvular vegetations. The subendocardial tissue beneath the thrombus showed fibroblastic proliferation and typical Aschoff cells.

5. Interventricular septum: Three blocks were cut and examined for the presence of Aschoff bodies. None was found.

Aorta: There was endarteritis with mural thrombosis, exactly similar in nature to the mural endocarditis and mural thrombosis seen in the heart. In addition, changes were also found in the adventitia and media. The adventitia showed patches of fibrinoid degeneration (deeper eosinophilic staining) of the collagen (Fig. 3) and increase of vascularity with heavy perivascular lymphocytic infiltration (Fig. 4). The outer half of the media showed also marked increase of vascularity with heavy perivascular lymphocytic infiltration (Fig. 3), or sometimes dense diffuse lymphocytic infiltration (Fig. 4). Areas of hyalin necrosis were found extending into the inner media from the intima (Fig. 5). The latter showed extensive foci of fibrinoid or hyalin necrosis, surrounded with fibroblastic proliferation (Fig. 5). Elsewhere, the intima showed fibroblastic proliferation with occasional Aschoff-like cells and diffuse infiltration with lymphocytes and plasma cells (Fig. 6). Areas of fibroblastic proliferation with large Aschoff-like cells also extended from the intima into the mural thrombus, accompanied with lymphocytic and plasma-cell infiltration (Fig. 7).

Fig. 6.

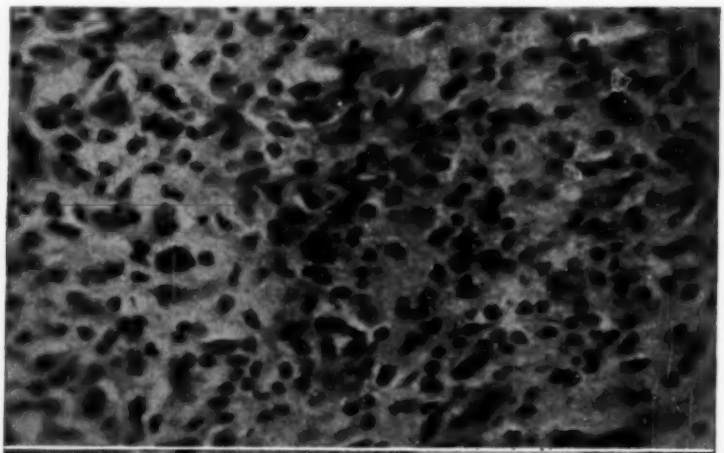

Fig. 7.

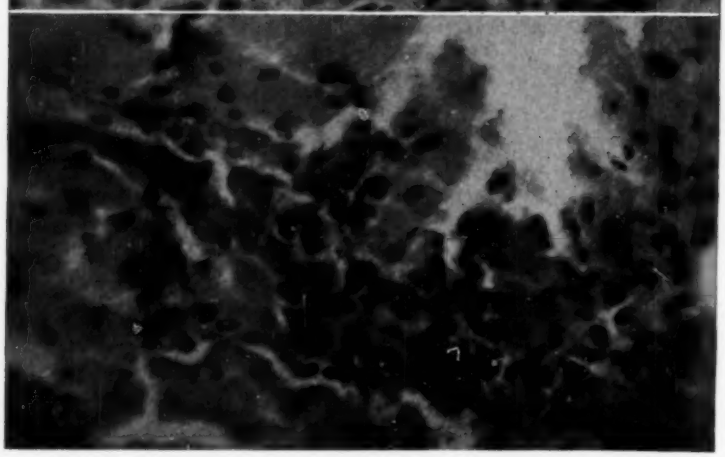

Fig. 6.—Intima of aorta showing fibroblastic proliferation with occasional large basophilic cells resembling Aschoff cells and lymphocytic and plasma-cell infiltration. ×200.

Fig. 7.—Mural thrombus of aorta (portion adjacent to aortic intima), showing, among the hyalinized fibrin of the thrombus, an area of fibroblastic proliferation with large Aschoff-like cells and lymphocytic and plasma-cell infiltration. ×200.

Iliac artery: The adventitia showed increased vascularity and perivascular lymphocytic infiltration. The outer margin of the media also showed similar infiltration. The inner elastic

lamella was reduplicated. The intima showed marked thickening due to increase of vascularity, fibroblastic proliferation, and lymphocytic infiltration. The lumen was occluded with a fresh, chiefly fibrinous thrombus (Fig. 8).

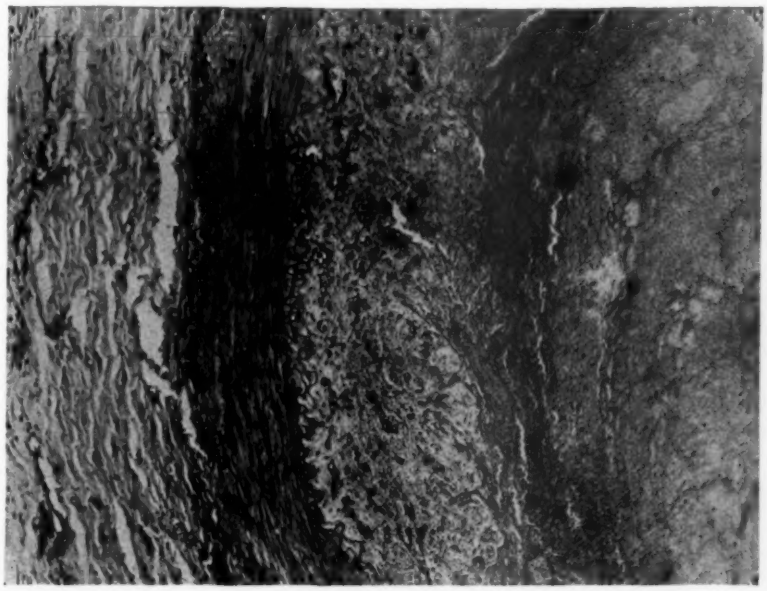

Fig. 8.—Iliac artery (right), with adventitia on the left and thrombus-filled lumen on the right, showing increased vascularity and perivascular cellular infiltration of the adventitia, cellular infiltration of the outer margin of media, splitting of internal vascular lamella, intimal thickening with increased vascularity, cellular infiltration and fibroblastic proliferation, and fresh thrombosis of lumen. ×80.

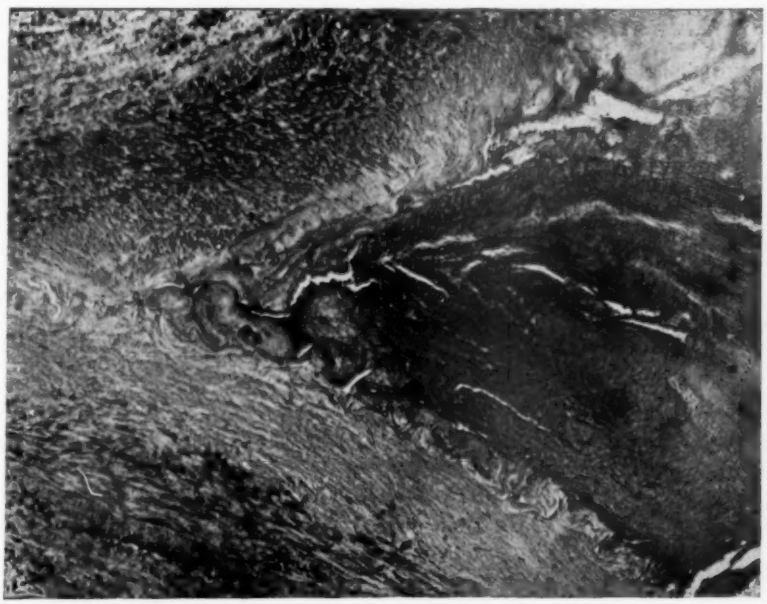

Fig. 9.—Femoral artery (right), showing cellular infiltration of adventitia (upper left and lower left fields of the picture), hyalin necrosis of the inner half of the muscular media, swelling, and partial destruction of the internal elastic lamella, and fresh thrombosis of lumen. ×80.

Femoral artery: It showed increase of vascularity and lymphocytic infiltration of the adventitia, hyalin necrosis of the inner half of the muscular media, swelling and partial destruction of the internal elastic lamella and a fresh, chiefly fibrinous thrombus occluding the lumen (Fig. 9).

Liver: A marked degree of chronic passive congestion was found.

Spleen: A typical fresh anemic infarct, surrounded by a hemorrhagic zone, was found in addition to chronic passive congestion of the red pulp.

Kidneys: The right kidney showed a healing infarct. The glomeruli in certain foci showed increase of cellularity (proliferative change) without demonstrable polymorphonuclear leukocytic infiltration. A few tubules contained red blood corpuscles. In the left kidney, small foci were found where the glomerular tufts showed slight leukocytic infiltration as well as endothelial and epithelial proliferation and where the tubules contained red blood corpuscles, leukocytes, and granular casts.

Anatomic Diagnoses.—Chronic and fresh rheumatic mural endocarditis of right ventricle and left auricle and ventricle with mural thrombosis; fresh and healed infarcts of spleen and kidney; chronic (rheumatic ?) myocarditis with scarring; marked cardiac hypertrophy and dilatation; chronic passive congestion of liver and spleen; acute rheumatic fibrinous pericarditis; acute rheumatic aortitis with mural thrombi; and rheumatic (?) iliac and femoral arteritis (right side) with thrombosis.

REVIEW OF THE LITERATURE

Tissue Changes in Arterial Walls Caused by Rheumatic Fever.—The tissue changes in the arterial walls produced by rheumatic fever were considered to represent a hyperergic reaction by Swift, Derick, and Hitchcock (1928),[1] and Klinge and Vaubel (1931)[2] shared this view. The latter considered the following changes in the arterial walls as being characteristic: (1) swelling of connective tissue ground substance with a variable degree of fibrinoid change; (2) hyperplasia of connective tissue cells with or without basophilia of the cytoplasm, accompanied by variable degrees of lymphocytic and leukocytic infiltration; and (3) hyalin scar formation with or without destruction of the elastic lamellae. Von Glahn and Pappenheimer[3] have described exudation of fibrin into and around the vessel wall, organization of fibrin with formation of new collateral channels within the thickened intima or occasionally within the muscular media, and distinct leukocytic, lymphocytic, and plasmocytic infiltration in the perivascular fibrous tissue. Edema, profuse cellular infiltration (Rae[4]), fibrinoid degeneration (Klinge[5]), necrosis (Rae,[4] Sacks[6]), liquefaction necrosis of muscle fibers (Rabé[7]), and scar formation (Pappenheimer and von Glahn[8]) have been found in the media of muscular arteries. Aschoff bodies have been seen in the adventitial fibrous tissue of the coronary arteries and in the fibrous tissue around the vasa vasorum in the adventitial sheath of the roots of the aorta and pulmonary artery.[9,10]

Parts of Arterial Tree Known To Be Affected by Rheumatic Fever.—Rheumatic lesions have been found in the coronary arteries (Karsner and Bayless,[9,11] Gross and Oppenheimer,[12] and Rae[4]), the roots of the pulmonary artery and aorta (Gross[10]), pulmonary artery (Raiche,[13] Paul,[14] Eiman and Gouley,[15] Kugel and Epstein,[16] McClenahan and Paul,[17] and Chiari[18]), aorta (Pappenheimer and von Glahn,[8,19] Perla and Deutch,[20] and Neiman[21]), innominate artery and carotid arteries (Heydloff[22]), coelic axis, superior mesenteric, and renal arteries (Pappenheimer and von Glahn[23]), arteries of the lungs, kidneys, colon, ovary, testis, and pancreas (von Glahn and Pappenheimer[3]), arteries of the kidney (Clawson,[24]

Baehr and Sacks[25]), and mesenteric arteries and small arteries in the hilum of the spleen (Perla and Deutch[20]).

Histopathology of Rheumatic Aortitis.—The changes found in the adventitia in the reported cases of rheumatic aortitis were lymphocytic and plasma-cell infiltration, either diffuse or around the vasa vasorum (Klotz[26]), with admixture of polymorphonuclear leukocytes which might even reach a predominating number,[19] intimal proliferation to sclerosis of the vasa vasorum,[8,9] general fibrosis or ringlike fibrosis around the vasa vasorum (Barnard[27]), swelling of collagen,[19] proliferation of fibroblasts with cytoplasmic basophilia and nuclear hypertrophy[19] or even with the formation of multinucleated cells,[19] and the presence of typical Aschoff cells and Aschoff nodules.[8,19,20]

The medial changes were penetration of the nutrient vessels from the adventitia into the media beyond the bondary between the outer third and the middle third of the media (Klotz[28]), diffuse and perivascular infiltration of plasma cells and lymphocytes (Klotz[28]), being particularly severe in the outer third of the media, often with destruction of the muscle fibers and elastic lamellae,[20] scar formation around the penetrating vessels,[8] and the presence of Aschoff-like cells arranged in rows between the elastic lamellae.[3] Gray and Aitken[29] described a dissecting aneurysm of the aorta, arising as a result of medial destruction.

The intimal changes were as follows: Perla and Deutch[20] described a case of macroscopic involvement of the aorta with fresh and organizing fibrinous plaque on the intima. The proliferating connective tissue cells at the base of the fibrin plaques presented a characteristic vertical orientation. Neiman[21] described three cases of verrucous aortitis or verrucous endarteritis of the aorta on top of intimal lesions characterized by patches of fibrinoid swelling and necrosis of the ground substance of the intima with proliferation of the adjacent fibrocytes. Morphologically, the verrucae were similar to those found on the cardiac valves in rheumatic endocarditis. Gross[10] also described fibroblastic proliferation of the intima and verrucous endarteritis in the roots of the aorta and pulmonary artery. Pappenheimer and von Glahn[30] believed that the aorta may be affected primarily by way of the intima as well as through the vasa vasorum.

Occurrence of Thrombosis in Rheumatic Arteritis.—Perry[31] found thrombosis of the left coronary artery in a child of 14 years. Leyden[32] found thrombosis of both coronary arteries in a case of acute rheumatic fever. MacCallum[33] found multiple thromboses of the coronary arterioles in severe cases of rheumatic fever. Karsner and Bayless[9] found the incidence of thrombosis of the coronary arteries to be markedly decreased after the third decade of life and stated that the thrombus was mural in the larger vessels and occlusive in the smaller ones, consisting, in the main, of either white blood cells, or fibrin, or both. Baehr and Sacks[25] found thrombosis of the arteries inside the kidney with extension into the main renal artery. The thrombosis was considered to be secondary to the arterial disease (endarteritis) (MacCallum,[33] Karsner and Bayless[9]), and blood culture studies showed that it bore no relation to bacteremia (Karsner and Bayless[11]). Romberg[34] found numerous venous thromboses in rheumatic fever; Karsner and

Bayless[11] found venous thrombosis in fourteen patients in the first three decades of life. Sacks[35] described thrombosis of the veins of the neck and upper extremity as an uncommon but authentic complication of rheumatic fever, and Poynton[36] reported a case of unusually extensive obliterative thrombosis of the superior vena cava and innominate, subclavian, internal and external jugular, axillary, and left inferior thyroid veins.

DISCUSSION

From the viewpoint of pathologic anatomy, the changes in the left auricle (mural thrombus consisting of hyalinized fibrin, with fibroblastic proliferation of the endocardium beneath the thrombus and presence of Aschoff cells), the parietal pericardium (exudation of hyalinized fibrin without leukocytes on the inner surface with typical Aschoff cells in the connective tissue beneath), and the aorta (hyalin necrosis of the collagen tissue of the intima, mural thrombi, presence of Aschoff-like cells and fibroblastic proliferation in the intima, and medial and adventitial changes similar to those described by Klotz, Pappenheimer and von Glahn, and Perla and Deutch in rheumatic aortitis) must be considered as being caused by rheumatic fever. It is somewhat unusual that there was rheumatic mural endocarditis of the right ventricle and left auricle and ventricle in the absence of valvular endocarditis, but recently we have seen a case of marked chronic fibrous mural endocarditis of the left auricle and ventricle, associated with only mild rheumatic mitral, aortic, and tricuspid valvular fibrous endocarditis, and there is no reason why mural endocarditis cannot occur alone. The age and sex of the patient also pointed to rheumatic fever. The urinary findings can be accounted for by the slight acute focal glomerulonephritis.

The iliac and femoral arteritis with thrombosis in this case is also considered by us to be on a rheumatic basis. For this view we present the following reasons:

1. Involvement of the iliac and femoral arteries by direct extension of the rheumatic lesion in the aorta is easily conceivable, and Heydloff has described rheumatic involvement of the innominate and carotid arteries which are topographically comparable to the iliac and femoral.

2. The pathologic changes of the said arteries (increase of vascularity and perivascular lymphocytic infiltration in the adventitia, lymphocytic infiltration of the outer margin of the media, hyalin necrosis of the inner half of the media, intimal thickening due to cellular infiltration and fibroblastic proliferation and fresh occlusive thrombosis) are in alignment with those found in rheumatic fever.

3. Thrombosis of both arteries and veins has been described in rheumatic fever, and Sacks has described thrombosis of the veins of the neck and upper extremity as an authentic complication of rheumatic fever. In our patient, the arterial thrombosis cannot be accounted for on the basis of septicemia or bacteremia, as blood culture was negative and as the infarcts of the spleen and kidney were due to emboli arising from the mural thrombi of the left auricle and ventricle and showed no sepsis.

4. There is no evidence of the presence in our patient of polyarteritis nodosa which is sometimes associated with rheumatic fever. A study of the histologic sections of the iliac and femoral arteries show no eosinophilic infiltration nor purulent infiltration of the adventitia, media, or intima. Moreover, polyarteritis nodosa involves arteries of the viscera rather than those of the limbs.

5. There is no evidence of Buerger's disease or thromboangiitis obliterans. For in Buerger's disease of this duration, we usually find the artery to be obstructed by an old well-organized thrombus with recanalization, or at least we expect to find this lesion at some level of the arterial tree. In the present case, both the iliac and femoral arteries showed occlusion by fresh, chiefly fibrinous thrombi. In Buerger's disease, the involvement of the arterial tree is segmental, while in our case the thrombosis was continuous in the iliac and femoral arteries.

The occurrence of gangrene as a complication of rheumatic fever has not, as far as the authors can find out, been reported in the medical literature and for this reason this paper is written.

SUMMARY

A case of gangrene of the right foot and leg, apparently due to rheumatic arteritis with thrombosis, is herein reported. No reference can be found in the medical literature as to the occurrence of gangrene as a complication of rheumatic fever. The histopathology of rheumatic aortitis and arteritis is reviewed.

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INTERVENTRICULAR SEPTAL DEFECT COMPLICATED BY PREGNANCY

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ACCURATE prognosis is difficult in cases of interventricular septal defect complicated by pregnancy. Two similar cases are presented here, one with autopsy proving the ante-mortem diagnosis.

Standard classification of heart disease does not appear reliable as a guide to the hazard involved. The two cases were considered to be in Class I B; one patient died in the seventh month of pregnancy of congestive heart failure while the second patient had an uneventful delivery. Kerr and Sodeman[1] report six patients with interventricular septal defects, having fourteen pregnancies. In nine cases the patients remained in Class I A throughout pregnancy. One patient changed from Class I A to Class IV C due to the development of post-partum heart disease. There were no deaths in this group. Roger's[2] oldest patient was a woman of 50 years who had borne four children and was leading an unrestricted life. Taussig[3] states that the prognosis is good in cases of small interventricular septal defects. Patients with this malformation usually lead long and active lives. Only in cases in which a high ventricular septal defect is so large that the arteriovenous shunt causes changes in the pulmonary vessels is the prognosis guarded. Marquis,[4] reporting on a study of four cases in early childhood, believes that once symptoms of circulatory failure have developed the prognosis must be considered poor.

CASE REPORTS

CASE 1.—L. B., a 28-year-old primipara, examined in May, 1949, was known to have had some type of heart disease since childhood. Cyanosis had been noted on exertion, such as playing tennis. Recently there was some dyspnea on exertion. She had noted palpitation and numbness of the fingers at times. Most of her childhood, like other children, she could run and play with no symptoms; only in recent years had she been compelled to limit exercise. In recent weeks she had noticed some pain in the gums and teeth that seemed to be brought on by exercise. She had had the usual diseases of childhood but never any serious illness. There was no past history of chorea or rheumatism. The tonsils had been removed. The pulse rate had always been about 90 per minute. The family history was noncontributory.

The physical examination revealed no cyanosis, no dyspnea at rest, and no clubbing. The pulse rate was 96 and the blood pressure 106/70 mm. Hg in the left arm, 112/80 mm. Hg in the right arm, and normal in the lower extremities. Eye grounds were thought to show some venous engorgement. The heart apex was in the fifth space at the midclavicular line. No thrills were noted. A Grade II systolic murmur was heard at the apex with the point of maximal intensity over the lower left sternum. It could be heard along the entire left border of the sternum and

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over to the right in the third and fourth intercostal spaces. The second pulmonic sound was accentuated. Fluoroscopic examination revealed a normal aorta, and a prominent pulmonary artery and conus. No definite ventricular enlargement was noted. The left auricle was not enlarged. There was no enlargement of the liver or spleen and no edema. Blood and urine examinations were normal. The arm-to-tongue circulation time with calcium gluconate was 15 seconds. The electrocardiogram had a rate of 96 per minute. The P-R interval was 0.12 second and the QRS, 0.08 second. The S wave in Lead I was 12 mm. deep, with a prominent S II. The "V" leads over the right ventricle showed R and R′ waves with a QRS of 0.10 and the nadir of R′ at 0.08 second. Leads over the left ventricle showed a QRS of 0.10 and the nadir of R was 0.04 second. Right ventricular hypertrophy and possibly some thickening of the left ventricle was diagnosed. A diagnosis was made of congenital malformation with an interventricular septal defect. She was advised that she could most likely have her baby without circulatory troubles but was advised against other pregnancies. The patient was not seen again until Aug. 12, 1949.

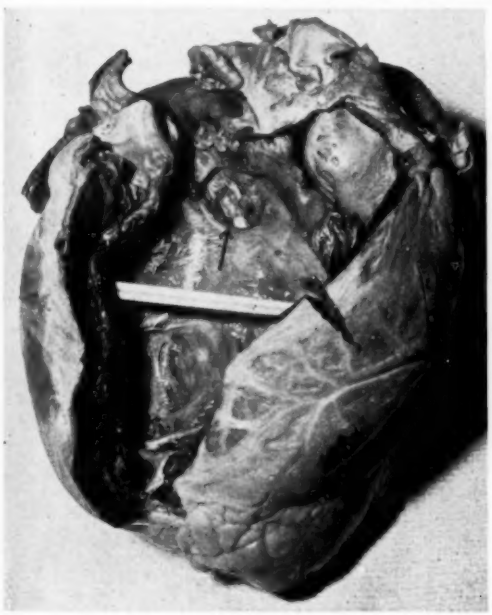

Fig. 1.

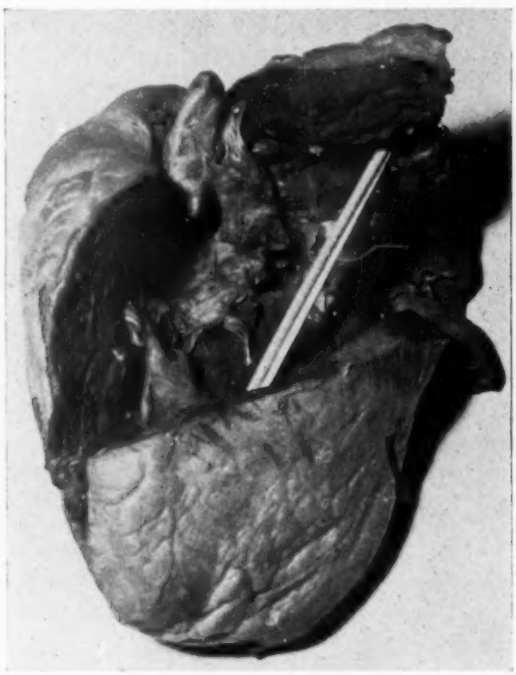

Fig. 2.

Fig. 1.—View of septum from the left ventricle. Arrow points to the interventricular defect.
Fig. 2.—View of septum from right ventricle. Arrow points to the interventricular defect.

She had been well up to seven days before this visit when she began having extreme exhaustion. This was soon followed by cyanosis and dyspnea. Some swelling of the ankles had been present for about one month. On examination the patient was found to be orthopneic and was showing marked cyanosis and edema of the lower extremities. She was immediately hospitalized and treated for congestive heart failure. She died less than twelve hours later.

Autopsy (A-78-49).—The heart was enlarged and weighed 510 grams. The pericardial sac was normal. The apex was formed by both ventricles. The left ventricle measured 2 cm. in thickness; the right ventricle, 1 cm. The mitral valve was 10 cm. in circumference; the tricuspid valve, 5.5 cm.; the aortic valve, 6 cm., and the pulmonic valve 5.6 cm. in circumference. The coronary arteries were normal. The endocardium was thin and shiny. There was an oval defect in the upper portion of the septum measuring 1 by 2.6 cm. The long axis of the interventricular septal defect was in an anteroposterior direction and pointing slightly downward at an angle of 30 degrees

from the base of the heart. The defect replaced the entire septum membranaceum and an area of about 1 cm. posteriorly to it. The lower margin of the defect was rounded and smooth. The upper margin as well as the anterior margin was sharp and the endocardium covered a narrow white ridge resembling valvular tissue. All valves were delicate. The great vessels were normal.

Microscopic examination: There was found marked hyperemia of the spleen, liver, kidneys, and gastrointestinal tract. The myocardium showed thickened muscle fibers with large irregular nuclei. This was true of both left and right ventricles.

Pathologic and anatomic diagnosis: Large congenital interventricular septal defect; left and right ventricular hypertrophy, and generalized passive congestion, edema, and hydrops due to right heart failure.

CASE 2.—C. S., a 21-year-old primipara, three months pregnant, was examined in February, 1951. The patient stated that she was born with heart disease and had always had some dyspnea on exertion. She had noted blueness of the lips when swimming. Her only important illness had been scarlet fever.

Physical examination revealed a radial pulse rate of 84. Blood pressure 120/70 mm. Hg. The heart did not appear enlarged on physical examination. There was a loud systolic murmur over the anterior chest, with the point of maximal intensity in the third left intercostal space. The murmur was transmitted down the left border of the sternum to the apex and over to the right of the sternum in the fourth intercostal space. The murmur could also be well heard over the left posterior chest region. Femoral pulses were normal and there was no edema. The arm-to-tongue circulation time, with calcium gluconate, was 9 seconds. Fluoroscopic examination showed a prominent pulmonary artery and the hilar vessels were enlarged and pulsating vigorously. In the left oblique view the pulmonary conus was seen to be enlarged but the left auricle was normal, and the right ventricle was thought to be enlarged. The left oblique view showed a normal aorta and no left ventricular enlargement. The electrocardiogram revealed a P-R interval of 0.16 second and a QRS interval of 0.06 second, a deep Q wave in Lead V_1, 0.02 second wide with a late R, suggesting right ventricular hypertrophy. It was advised that she start and continue a low sodium diet with restricted exercise, and that she return for circulation time tests at regular intervals. The patient did not return for examination until May 18, the seventh month of pregnancy. There was then no subjective symptoms except some dyspnea on slight exertion. The radial pulse rate was 108 and the blood pressure 110/80 mm. Hg. The murmur was accentuated. The arm-to-tongue circulation time was 7 seconds. A ballistocardiogram suggested an increased stroke volume. The patient had an uneventful delivery on July 22, 1951.

REMARKS

Comparison of these two similar case reports shows one point of important difference. The arm-to-tongue circulation time in the first examination was 15 seconds in Case 1, and 9 seconds in Case 2. Manchester and Loube[6] report a study of the arm-to-tongue circulation time in normal pregnant women. It was demonstrated that the blood velocity will normally increase from trimester to trimester. It is doubtful then if one should consider 15 seconds as a normal circulation time for the fourth month of pregnancy. Consideration of the two cases suggests that the circulation time may be a sensitive and reliable guide to early recognition of right heart failure in this type of case. Using the standard classification of heart disease, one would hardly expect Case 1 to have a sudden onset of right heart failure and death, while Case 2 presented no symptoms of failure throughout pregnancy. Further experience may indicate the circulation time as a reliable guide to prognosis in this particular type of abnormality.

Appreciation is expressed to Siegfried Werthammer, M.D., for his help and advice, especially for the pictures and post-mortem report.

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SUBACUTE BACTERIAL ENDOCARDITIS COMPLICATED BY INTERMITTENT COMPLETE HEART BLOCK AND STOKES-ADAMS ATTACKS

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COMPLETE heart block is a rare complication of subacute bacterial endocarditis. This uncommon association occurred in the patient described below. His record is reported because of its rarity and because of the interesting clinical picture which was presented.

CASE REPORT

T. H., a 35-year-old laborer, was admitted to the hospital in February, 1951, with attacks of nocturnal dyspnea. As a child of 3 months he had had an illness which was called rheumatic fever but about which he was unable to give further information. Later in childhood he had three attacks of pneumonia but no other major illnesses.

He remained well until he was discharged from the Army in 1940, following five months of service. After leaving the Army he noticed the gradual onset of dyspnea on exertion. This became progressively worse, especially in the last year. Despite this symptom he did heavy work as a laborer until two weeks before his admission. He then developed attacks of nocturnal dyspnea and, following a more severe attack of this, accompanied by cough and blood-stained sputum, he was admitted to hospital.

On examination, there was found clubbing of the fingers and toes. The arterial pulse had a rate of 43 per minute and its wave form was bisferious. The internal jugular veins showed irregular "cannon waves" (Fig. 2). The blood pressure was 120/90 mm. Hg. The apex beat was in the sixth left intercostal space, 4½ inches to the left of the midline, and the character of the cardiac impulse suggested left ventricular hypertrophy. There was a basal systolic thrill which was maximal beneath the third right costal cartilage and which was conducted into the neck. On auscultation at the apex the intensity of the first sound was variable, the second sound was single, and an inconstant sound, which was thought to be an auricular sound (Fig. 2), occurred between the second and first sounds. In the aortic area no sounds were audible but there was a loud to-and-fro murmur. The harsh systolic element was best heard in the second right intercostal space in the parasternal line and was conducted into the neck. The blowing diastolic element was best heard in the fifth left intercostal space in the parasternal line. No mitral diastolic murmur was heard.

Basal râles were present in the chest. The spleen was just palpable, but there were no petechial hemorrhages in the skin or retinae.

A diagnosis was made of aortic stenosis and incompetence, complete heart block, subacute bacterial endocarditis, and left ventricular failure. A blood culture was taken which later grew a *Streptococcus viridans*, and treatment was started with penicillin and mersalyl.

An electrocardiogram taken on the day after admission confirmed the diagnosis of complete heart block (Fig. 1). A simultaneous recording of the jugular phlebogram, the electrocardiogram, and the phonocardiogram demonstrated graphically the relationships between the complete heart block, the venous cannon waves, the auricular sounds, and the variable first heart sound. (Fig. 2.)

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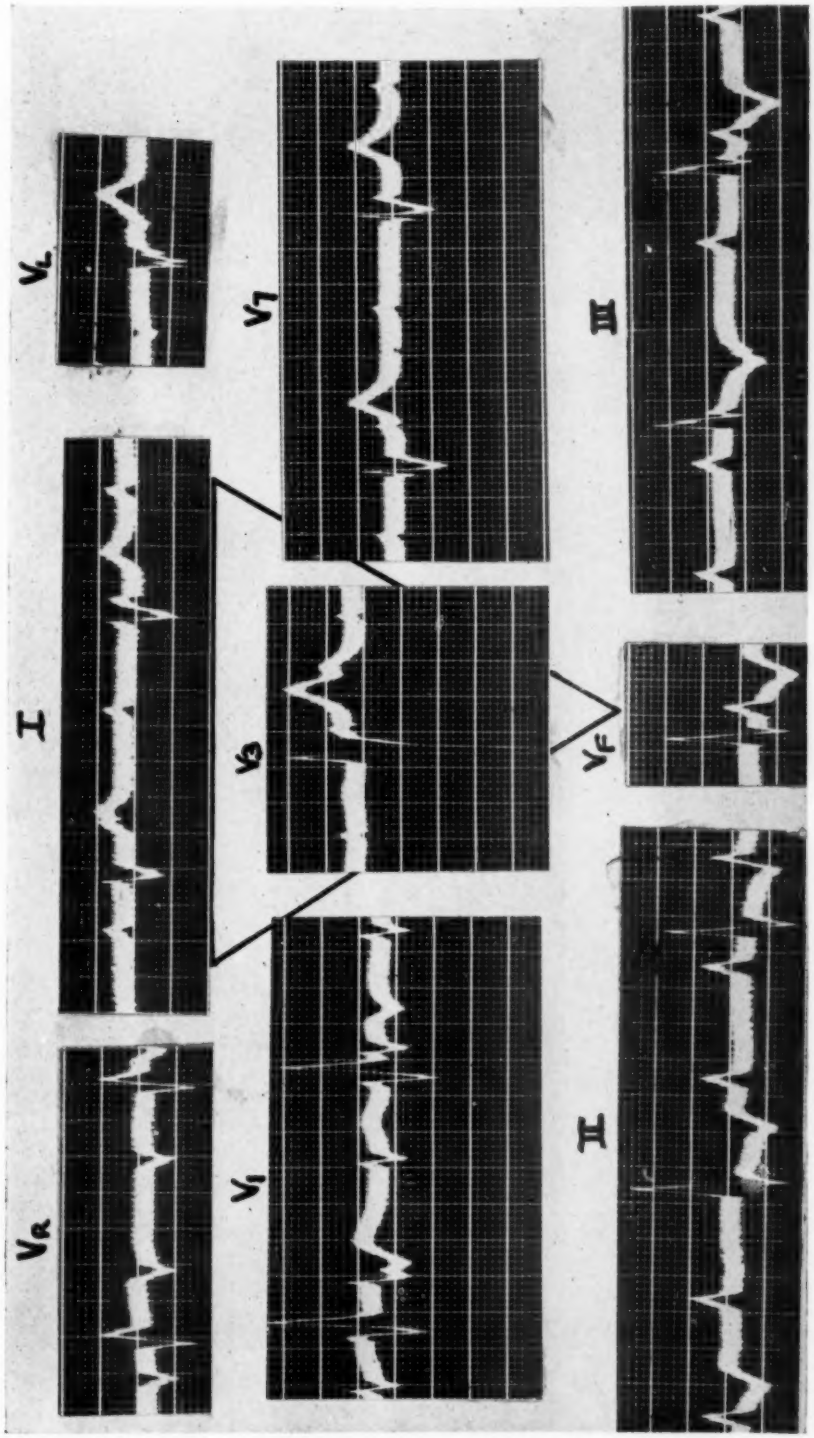

Fig. 1.—Electrocardiogram on admission showing complete heart block and a right bundle branch block pattern in the ventricular complexes. Time, 0.2 second and 0.04 second.

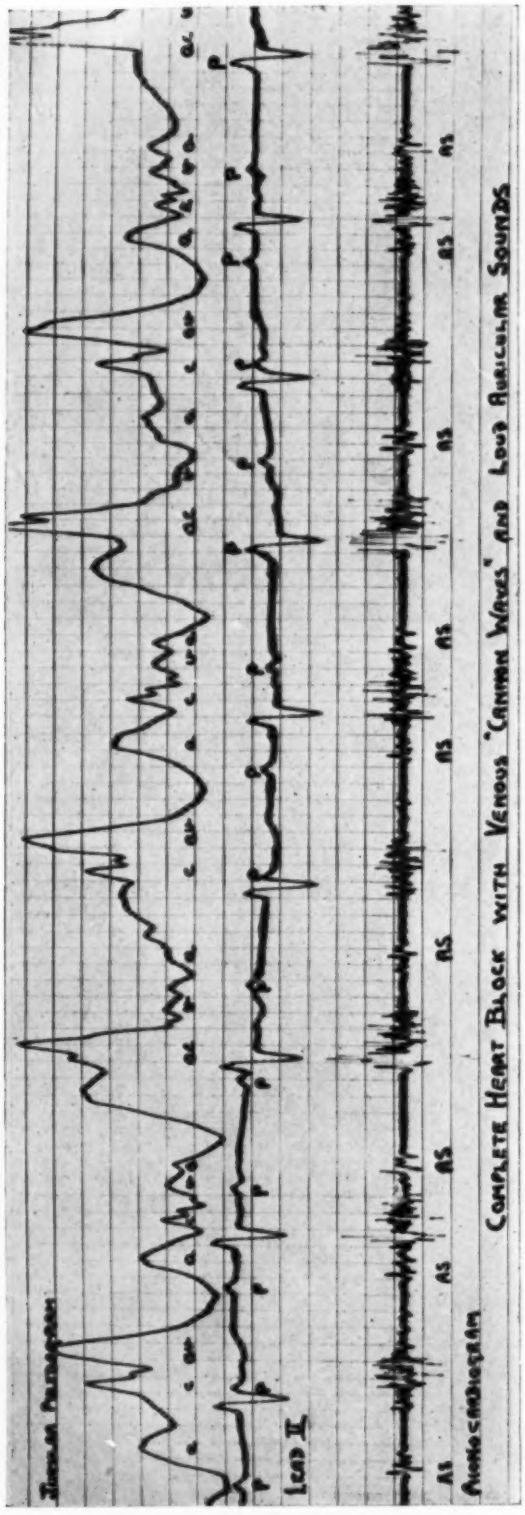

Fig. 2. Simultaneous recording of the jugular venous phlebogram; Lead II of the electrocardiogram and the apical phonocardiogram. Time 0.1, second. For description, see text.

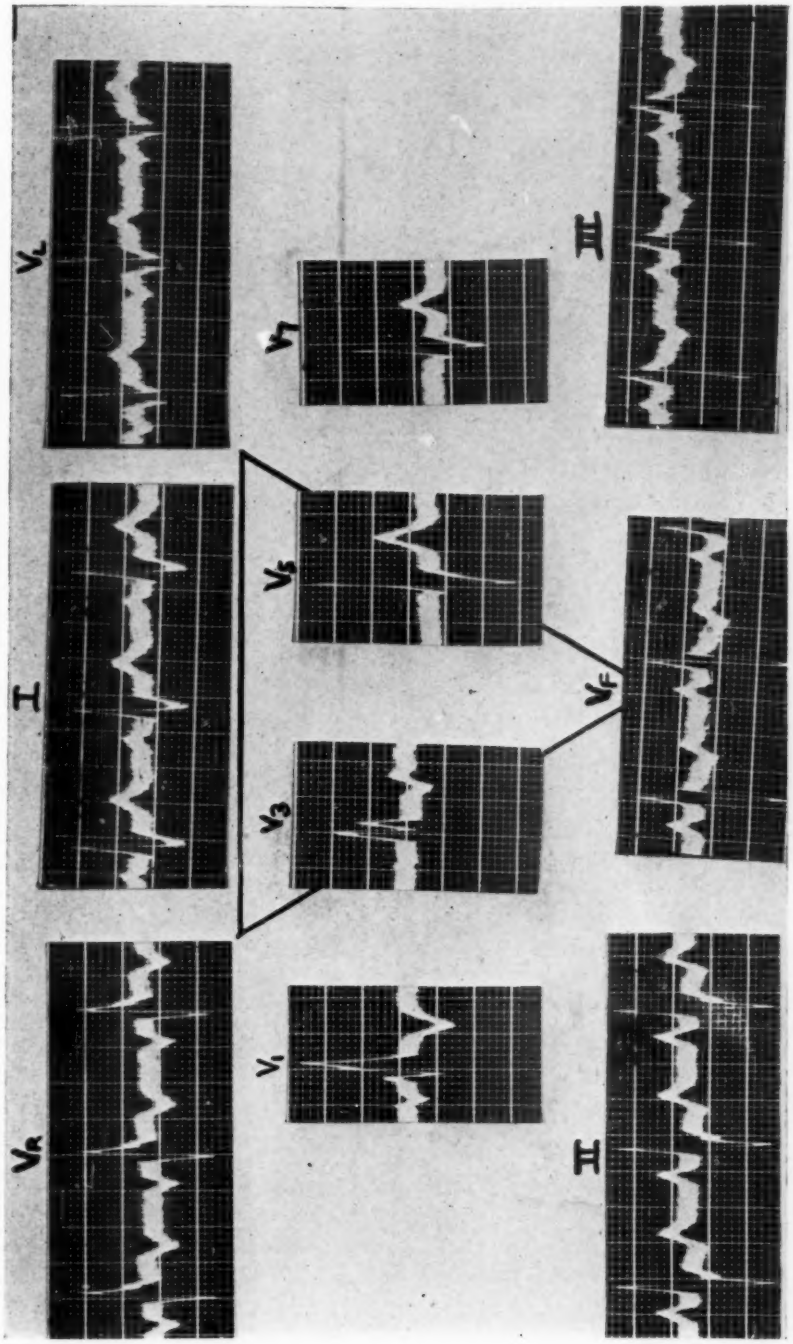

Fig. 3.—Electrocardiogram showing sinus rhythm with a right bundle branch block pattern in the ventricular complexes. Time, 0.2 second and 0.04 second.

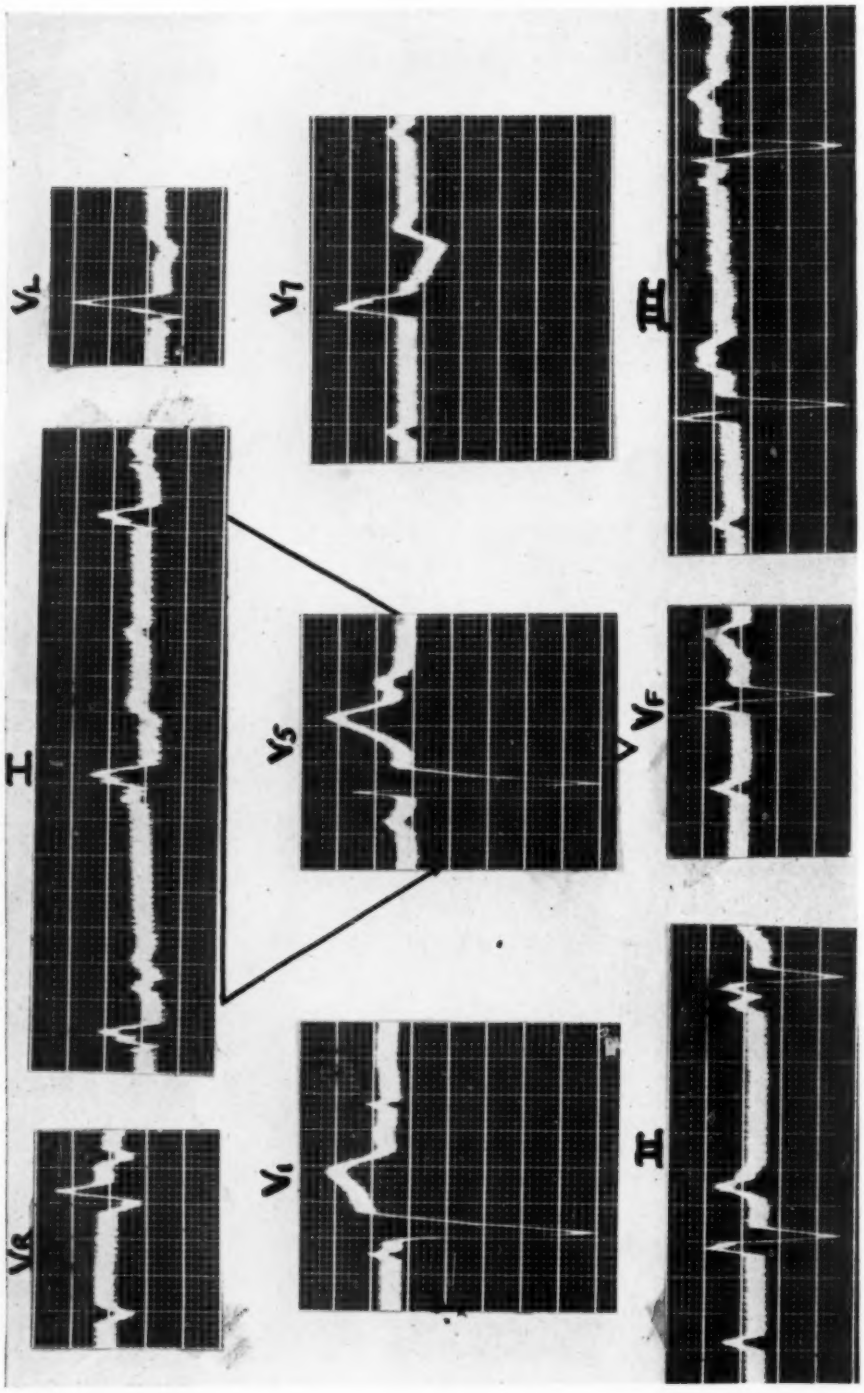

Fig. 4.—Electrocardiogram showing complete heart block with a left bundle branch block pattern in the ventricular complexes. Time, 0.2 second and 0.04 second.

Progress under treatment was not uneventful. The symptoms of left ventricular failure disappeared satisfactorily but after four weeks' therapy a new complication appeared. The rhythm of the heart began to alternate between complete heart block and sinus rhythm, and these changes of rhythm were accompanied by Stokes-Adams attacks. For these attacks ½ grain ephedrine was given three times a day and although the changes of rhythm continued these changes were no longer accompanied by attacks of unconsciousness.

Electrocardiograms taken during this period confirmed this alternation between sinus rhythm and complete heart block. During the periods of sinus rhythm the ventricular complexes showed the pattern of right bundle branch block (Fig. 3). During the periods of complete heart block the ventricular complexes were sometimes of the right bundle branch block pattern (Fig. 1) and sometimes of the left bundle branch block pattern (Fig. 4).

Four days after the onset of the Stokes-Adams attacks a pulmonary infarct developed. Intermittent intravenous heparin injections were given for this complication which subsequently cleared uneventfully. After six weeks' treatment with three-hourly intramuscular injections of 250,000 units of penicillin, the patient's general condition had improved considerably and he had no symptoms while resting in bed. Blood cultures were repeated and these were sterile. He was then gradually mobilized and three weeks later was discharged from the hospital. During his last two weeks in the hospital he appeared to have uninterrupted sinus rhythm.

After discharge he continued to feel that he was improving, but during his first week at home he had two attacks of unconsciousness. When he was seen for review, a month after his discharge, he again had complete heart block but there was no indication of an active infection. Three weeks later, however, he was readmitted with a relapse and rapidly succumbed.

At autopsy an aortic stenosis was found with recent gross vegetations on the aortic valve. There were numerous petechial hemorrhages throughout the myocardium but there was no macroscopic evidence of a gross lesion of the atrioventricular node or ventricular bundles. The mitral valve appeared normal.

DISCUSSION

The patient reported above presented two main points of interest: First, there was the association of subacute bacterial endocarditis with intermittent complete heart block and Stokes-Adams attacks. Second, there was a perfect demonstration of the signs of complete heart block, of which a graphic record was obtained.

In reported series of cases of bacterial endocarditis the occurrence of heart block and Strokes-Adams attacks has been rare. In a series of 123 cases Perry[1] described a single case of heart block associated with Stokes-Adams attacks. In this patient the infection occurred on an interventricular septum and had spread to involve the aortic valve. Another patient in this series showed partial heart block with occasional dropped beats. Saphir and his associates,[2] studying seventy-six fatal cases of bacterial endocarditis, reported that complete heart block had been present in only a single case. Cates and Christie,[3] reviewing 442 cases studied on the Medical Research Council's "Penicillin Trial," reported a single case with varying heart block and noted that, "heart block developed in another patient during the treatment of a second attack of endocarditis."

A similar impression of the rarity of the association of heart block and subacute bacterial endocarditis is formed from a review by Kay[4] of 100 cases of complete heart block in which no case was associated with subacute bacterial endocarditis.

In the patient reported above the subacute bacterial endocarditis had affected the aortic valve, which was stenosed from an old rheumatic lesion. The

association of complete heart block and rheumatic aortic stenosis is not unknown, and in this patient the development of bacterial endocarditis may have been no more than coincidental with a complete heart block occurring as a natural sequence of the chronic rheumatic carditis. Against this view is the observation that during penicillin therapy the complete heart block disappeared and sinus rhythm was established.

A graphic record of the physical signs associated with the complete heart block is shown in Fig. 2, which records simultaneously the jugular venous phlebogram, Lead II of the electrocardiogram, and the apical phonocardiogram. The phlebogram demonstrates the presence of venous cannon waves. These are produced by the auricle contracting against closed atrioventricular valves and hence they are seen to occur whenever auricular and ventricular systole coincide, or, in other words, whenever P falls between the beginning of the Q wave and the end of the T wave. From the record it appears that the greatest cannon waves are produced when auricular systole coincides with early ventricular systole, producing an apparent fusion of the "a" and "c" waves of the phlebogram, as is shown with the sixth and ninth recorded ventricular systoles. In the apical phonocardiogram the auricular sounds (A.S.) are clearly recorded and they occur 0.1 second after the onset of the P wave. The variable intensity of the first heart sound is also obvious. It can be seen that the loud sounds occur when the P-R interval is short, as with the third ventricular complex, and that the soft sounds occur when the P-R interval is long, as with the seventh ventricular complex. This relationship between the fluctuation of the intensity of the first heart sound and the P-R interval in complete heart block, as well as in other conditions, has been well described by Levine and Harvey.[5]

SUMMARY

A patient is described in whom subacute bacterial endocarditis is associated with complete heart block and Stokes-Adams attacks. A graphic description is given of the important physical signs.

I would like to thank Professor C. H. Stuart-Harris for permission to report this case. The patient was under his care.

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PRONESTYL (PROCAINE AMIDE) THERAPY IN PAROXYSMAL VENTRICULAR TACHYCARDIA

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PRONESTYL Hydrochloride (procaine amide) is a new drug in the therapy of paroxysmal ventricular tachycardia. The first publication written by Mark and associates,[8] involving the use of this medication, appeared in January, 1950. Since that time, several articles have been published concerning its use in ventricular tachycardia. We wish to present a case of paroxysmal ventricular tachycardia with atrioventricular interference and dissociation that was successfully treated with intravenous Pronestyl and later maintained on oral dosages of this medication.

CASE REPORT

The patient, a 71-year-old woman, was admitted to Goldwater Memorial Hospital on Nov. 7, 1947, from a nursing home. Unfortunately there was no accompanying transcript. Several months previously the patient experienced a cerebrovascular accident with resultant motor aphasia and right hemiplegia. On admission, physical examination revealed an obese mesomorphic white woman who was in no apparent distress. The pulse was 108 per minute; blood pressure was 140/70 mm. Hg bilaterally. Right facial paresis and right-sided hemiplegia with a clonus of the right ankle were present. The rest of the physical examination, including cardiac consultation, was negative. Laboratory findings included a red blood count of 3.6 million, hemoglobin of 11.5 Gm., white blood count of 8,500 with 78 per cent polymorphonuclear cells, blood sugar of 89 mg. per cent, blood urea nitrogen of 15.5 mg. per cent and a negative blood Mazzini. The electrocardiograph was interpreted as showing evidence of an old anteroseptal wall infarction (Fig. 1).

An interval electrocardiogram in August, 1948, had revealed the same pattern as the one taken nine months previously. Except for a mild upper respiratory infection in April, 1949, which responded to symptomatic therapy, the hospital course was uneventful. On March 22, 1950, the patient was found to have urinary retention. A causative factor was not found. She was catheterized and then given 1 c.c. of Prostigmine Bromide Methylsulfate (1:2000) by injection. One hour later the patient experienced a cold sweat with vomiting. The blood pressure dropped to 80/60 mm. Hg and a gallop rhythm was noted. Atropine (1/150 grain) was given without relief.

An electrocardiogram revealed a tachycardia which was thought to be ventricular with atrioventricular interference and dissociation. Supraventricular tachycardia was considered in the interpretation (Fig. 2). It was thought that the patient might have had an acute infarction superimposed on the previously mentioned anteroseptal wall infarction or Prostigmine poisoning due to sensitivity. Carotid sinus pressure had no effect upon the tachycardia. Quinidine and later ouabain were administered without effect. Finally, Pronestyl, 500 mg. dissolved in 20 c.c. of distilled water, was given intravenously. Within three minutes the rate began to slow and after eight minutes there was reversion to a regular sinus rhythm. The pulse became 80; the blood pressure rose to 110/80 mm. Hg.

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The course was uneventful until January 13, 1951, when the pulse rate rose to 160 per minute. The electrocardiogram revealed the same pattern as that noted on March 22, 1950. Carotid sinus pressure and eyeball pressure failed to alter the tachycardia. Intravenous digitalization also had no effect. Quinidine was given every two hours until the patient experienced nausea and vomiting. A total of 27 grains was given in ten hours. Shortly thereafter the tachycardia reverted to a regular sinus rhythm at a rate of 75 per minute. No further medications were given.

The pulse rate remained between 76 and 80 per minute until Feb. 19, 1951, when the patient was found to have a tachycardia of 140 to 160 per minute. The electrocardiogram again revealed the same changes. Carotid sinus pressure had no effect. Syrup of ipecac was given until vomiting ensued, but to no avail. Quinidine was given at two-hour intervals, until a total of 33 grains was given. Approximately twelve hours later, the rate suddenly dropped to 80 per minute with a regular sinus rhythm (Fig. 3). The following day the patient became febrile and physical findings revealed an area of consolidation in the right lower lobe. There was satisfactory response to antibiotic (penicillin) therapy.

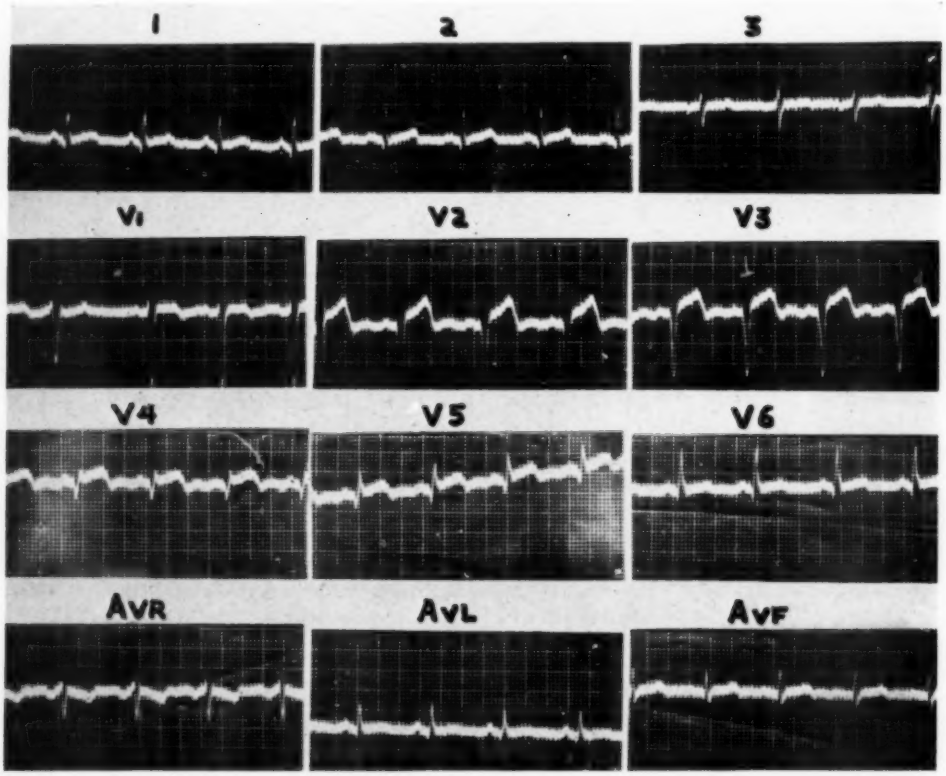

Fig. 1.—Admission electrocardiogram. This is interpreted as showing evidence of an old anterolateral wall infarction. (M. F., 11/13/47.)

On March 14, 1951, the patient again developed a tachycardia with a rate of 156 per minute. Electrocardiograms revealed the same type of mechanism. The patient received 15 grains of quinidine in four hours without response. Pronestyl, 300 mg. dissolved in 10 c.c. of water, was given intravenously. Within five minutes the rate dropped to 135 per minute. One-half hour later, a second dose of 300 mg. of Pronestyl dissolved in 10 c.c. of water was administered intravenously. Five minutes later, the rate dropped to 88 per minute with a regular sinus rhythm (Fig. 4). On April 17, 1951, the patient developed a pulse rate of 166. Pronestyl, 300 mg. in 15 c.c. of water, was given intravenously. There was a reversion to regular sinus rhythm in one and one-half minutes.

On April 27, 1951, the patient experienced another episode of tachycardia with a rate of 152 per minute. A total of 1.2 Gm. of Pronestyl was given in three divided doses over a period of two hours without any effect. This was the first occasion that Pronestyl had no effect on the tachycardia. Quinidine (6 grains) was given every hour, but after the fourth dose the patient began vomiting and the drug was discontinued. Three hours after the last dose of quinidine, Pronestyl, 500 mg. in 5 c.c. of water, was given intravenously and almost immediately the rate dropped from 150 to 100 per minute but the abnormal mechanism persisted. An additional amount of Pronestyl, 250 mg. in 5 c.c. of water, was given intravenously. This caused the rate to be maintained at about 100 per minute but there was no change in the mechanism. An additional 275 mg. of Pronestyl was given intravenously but without any effect. The patient was then given four capsules (1 Gm.) of Pronestyl in divided doses prior to retiring. In the morning, approximately six hours later, the rhythm was found to be regular at a rate of 94 per minute (Fig. 5). The patient was then placed on oral capsules of Pronestyl (one capsule three times a day) in an effort to determine a maintenance dose.

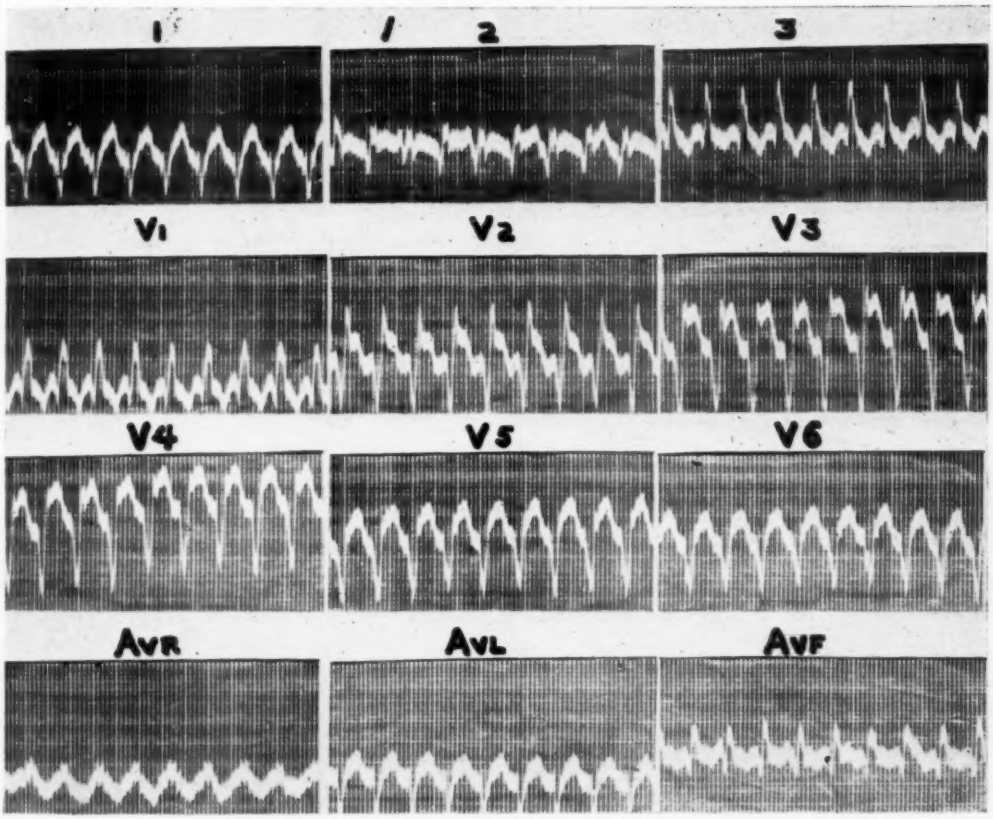

Fig. 2.—Initial episode of tachycardia one hour after an injection of 1 c.c. of Prostigmine (1:2000). Patient was in shock. Ventricular tachycardia with atrioventricular interference and dissociation. Supraventricular tachycardia was also considered in the interpretation. Reverted to RSR in eight minutes after 500 mg. of Pronestyl was given intravenously. (M. F., 3/22/50.)

On May 2, 1951, the ventricular tachycardia, despite oral therapy of one capsule of Pronestyl three times a day, returned to a rate of 152 per minute. Pronestyl, 500 mg. in 5 c.c. of water, was given intravenously, and in approximately two minutes there was reversion to regular sinus rhythm at the rate of 100 per minute. Seven minutes later the tachycardia reappeared. Pronestyl, 250 mg. in 5 c.c. of water, was given intravenously. In less than twenty-five minutes, there was a reversion to regular sinus rhythm. As the maintenance dose was insufficient, Pronestyl was increased to two capsules three times a day.

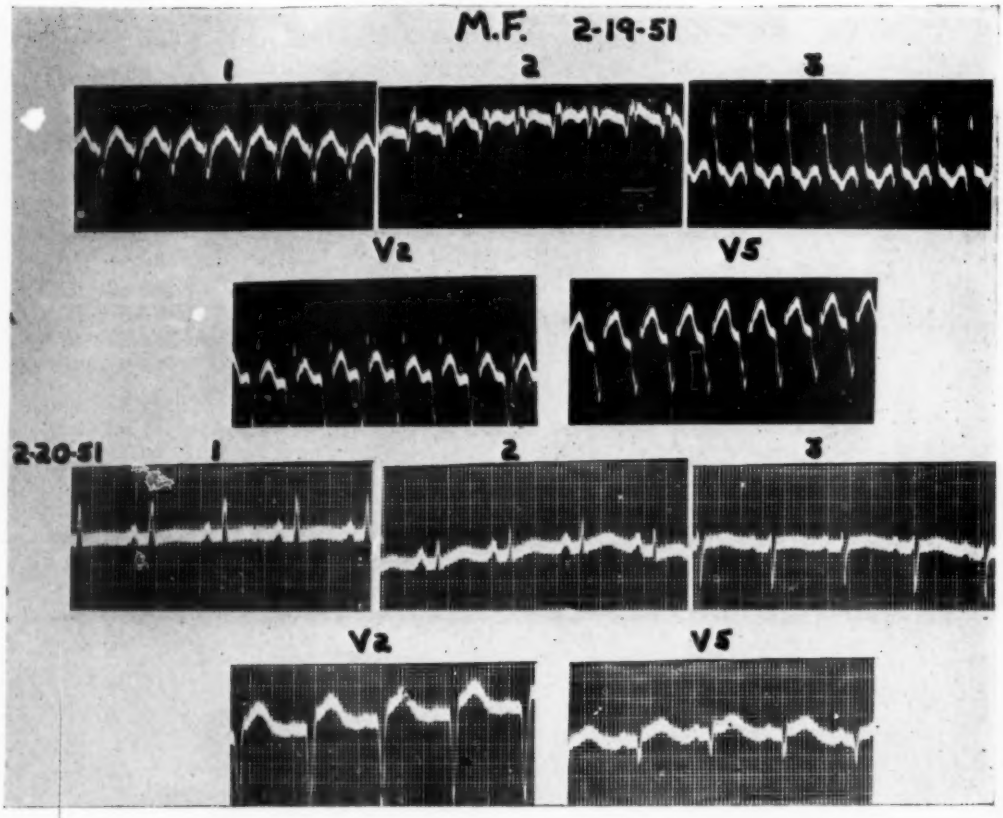

Fig. 3.—Recurrence of tachycardia. Treated with quinidine, total dosage of 33 grains. Twelve hours after last dose, the rhythm was found to be regular. (M. F., 2/19/51 and 2/20/51.)

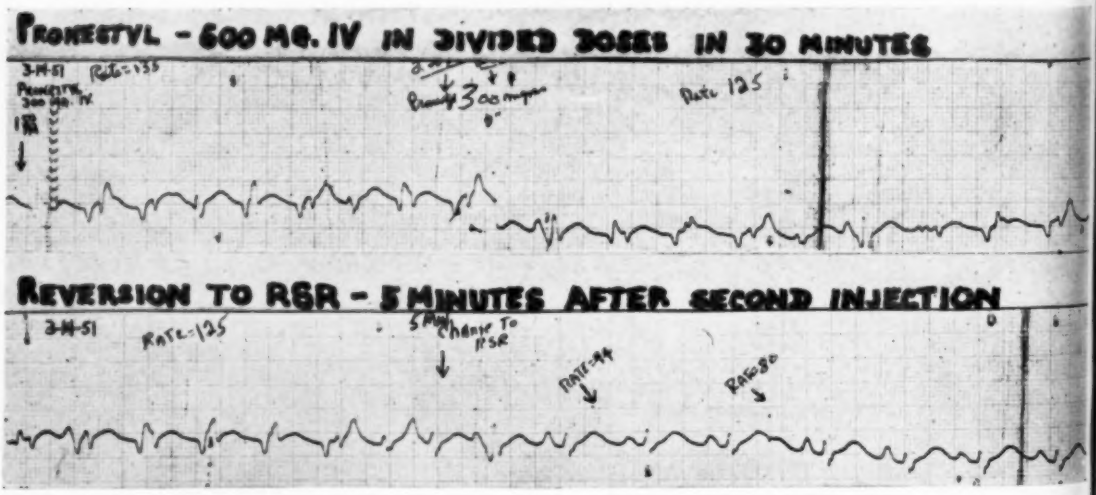

Fig. 4.—Recurrence of tachycardia. Pronestyl given in divided doses one-half hour apart. Return to a regular sinus rhythm five minutes following the second dose. (M. F., 3/14/51.)

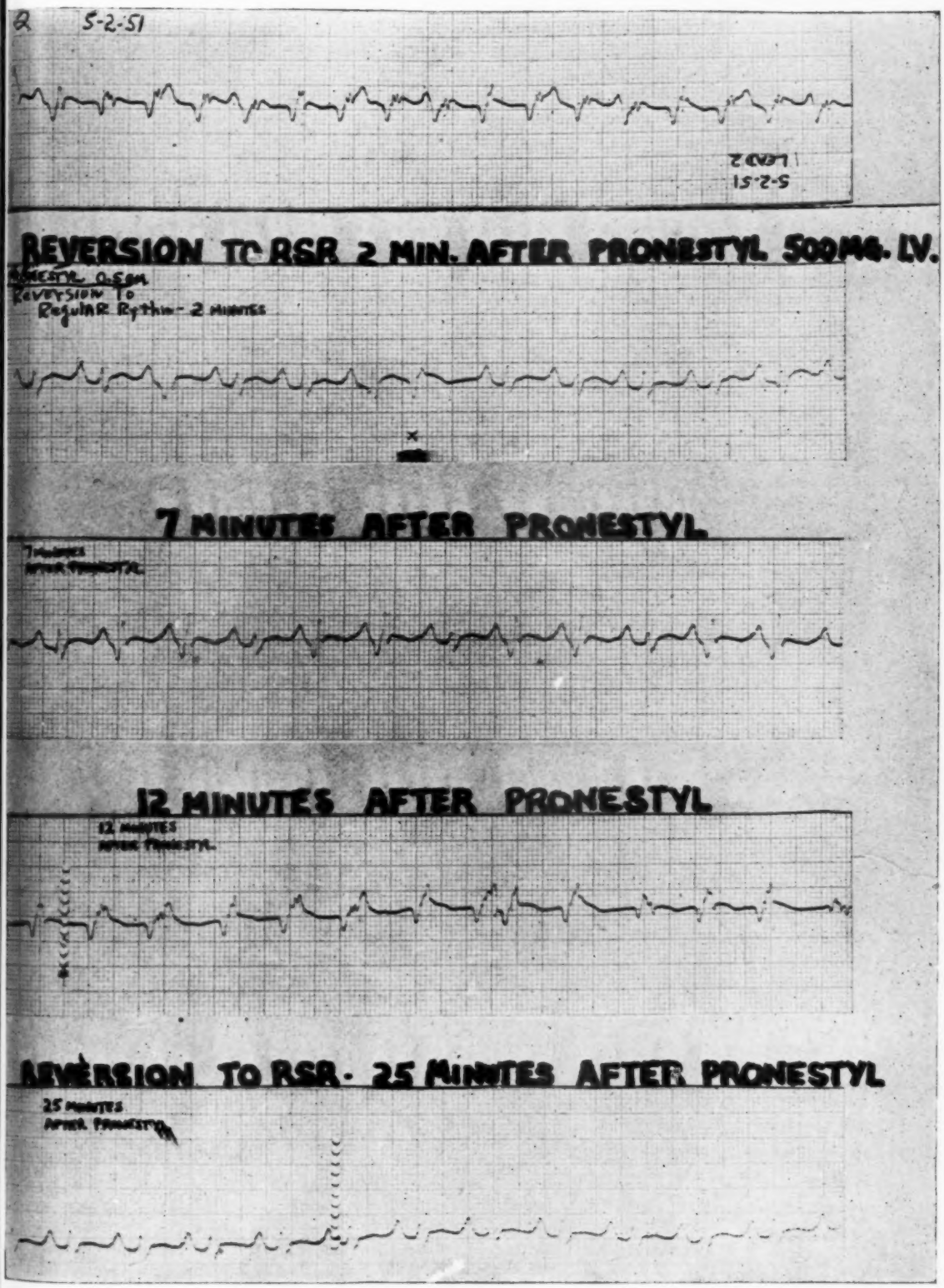

Fig. 5.—Recurrence of tachycardia while maintenance oral dosage of Pronestyl was being determined. Reversion to regular sinus rhythm two minutes after Pronestyl was given intravenously. The tachycardia reappeared in seven minutes. There was reversion to a regular sinus rhythm again after a second intravenous dose of Pronestyl was given. (M. F., 5/2/51.)

On May 3, 1951, the tachycardia reappeared at a rate of 160 per minute. Pronestyl, 500 mg. in 5 c.c. of water, was given intravenously. In one minute regular sinus rhythm was restored at a rate of 100 per minute. However, after seven minutes, the tachycardia reappeared. The patient was given sedatives without effect. Pronestyl capsules, one every four hours, had no effect. On May 6, 1951, another dose of Pronestyl, 500 mg. in 5 c.c. of water, was given intravenously with a slowing of the rate from 136 to 124 per minute. Eight minutes later, Pronestyl, 300 mg. in 3 c.c. of water, was given intravenously and in approximately two minutes there was a reversion to a regular sinus rhythm. The tachycardia reappeared in five minutes and then reverted to a regular sinus rhythm twelve minutes later. The maintenance dose was then increased to three capsules every four hours, day and night, and the heart remained in regular sinus rhythm from that date (period of 2 months).

The dosage was reduced to two capsules every four hours with the following regime: Pronestyl, two capsules (0.5 Gm.) every four hours if pulse is under 80, and three capsules (0.75 Gm.) if pulse is over 80. The tachycardia did not recurr.

The patient had an uneventful course from the time of her last bout of tachycardia (May 6, 1951) until July 1, 1951. At this time it was found that she had a fever of unknown etiology (102-103° F.) for several days. The red blood count was 3.9 million; hemoglobin was 12 Gm.; the white blood count was 10,000 with 80 per cent polymorphonuclear cells, 18 per cent lymphocytes, and 2 per cent monocytes. A course of penicillin, 500,000 units twice a day, was started. On July 5, 1951, a blotchy, purpuric rash, which extended from the base of the left thumb to the axilla, on the inner aspect of the left arm, was noted. The pulse rate was 140 per minute. Shortly afterwards, the rate dropped to 110 per minute and the purpuric rash suddenly appeared to be scarlet red. As the pulse rate soon rose to its previous level, the patient was given quinidine orally, a total of 42 Gm. in twenty-four hours. The following day, the electrocardiogram revealed a regular sinus rhythm. A dermatologist called in consultation stated that the lesion on the left upper extremity was a "drug rash."

On July 12, 1951, the patient became afebrile, the pulse was 80 per minute and regular, but the blood pressure had dropped to 72/36 mm. Hg. The white blood count was 1,600 with 78 per cent lymphocytes. Platelet count was 150,000. Urinalysis revealed specific gravity of 1.011, albumin two plus, no sugar, great quantity of granular casts, and numerous red and white blood cells. Ileus was present. There was no abdominal tenderness, spasm, or rigidity. A rectal tube and enema failed to provide any relief. A blood transfusion was given. A repeat blood count on the following day confirmed the previous ones. The pulse was 88 per minute and regular. The patient died quietly shortly thereafter. Chest plates on the day prior to and the day of death revealed only pulmonary congestion.

COMMENT

A case of paroxysmal ventricular tachycardia with atrioventricular interference and dissociation has been presented. Shock and the tachycardia occurred one hour after an injection of Prostigmine. Sensitivity to Prostigmine must be considered as a possible inciting factor. Atropine, in a single small dose, was given without effect.

Each episode of tachycardia was treated with intravenous Pronestyl (250 to 500 mg.) while an oral maintenance dose was being determined. This was established by the utilization of one capsule (0.25 Gm.) three times a day, two capsules four times a day, and then one capsule every four hours, which all proved ineffective in preventing the recurrence of the paroxysmal episodes. When the dosage of three capsules (0.75 Gm.) every four hours was reached, the tachycardia failed to recur. The oral tolerance maintenance dose of three capsules every four hours for five doses daily (6 A.M. to 10 P.M.) would seem to have been established.

It would seem that the intravenous route of administration of Pronestyl during paroxysmal episodes of ventricular tachycardia would be the therapy of choice while the oral maintenance dose is being determined. A major point of interest was the recurrence of the tachycardia on three occasions, seven to ten minutes after restoration of regular sinus rhythm, with subsequent reversion to a regular rhythm shortly afterwards.

It is believed that Pronestyl given in large doses over a prolonged period of time may have caused the blood dyscrasia noted in this patient. Further data are necessary to prove this. Nevertheless, the tendency for procaine amide to produce an agranulocytosis should always be borne in mind.

SUMMARY

A case of paroxysmal ventricular tachycardia with atrioventricular interference and dissociation refractory to quinidine and other methods of treatment was reverted with Pronestyl (procaine amide hydrochloride). A method of treatment outlining oral maintenance dosage has been described. The drug appeared to be effective in ventricular tachycardia and deserves further trial. Possible toxicity, producing agranulocytosis and purpura, has been noted.

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TETRALOGY OF FALLOT WITH SUBACUTE BACTERIAL ENDOCARDITIS. SUCCESSFUL TREATMENT WITH CHLOROMYCETIN

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SUBACUTE bacterial endocarditis before the sulfa-antibiotic era was therapeutically a hopeless disease in which recovery was rarely observed. With the advent of the sulfonamides and then penicillin, cures began to be reported, so that today a recovery rate between 50 and 75 per cent may be expected.[1] However, there are cases which are resistant to penicillin, and it is in these that the newer antibiotics, aureomycin, Chloromycetin, bacitracin, terramycin, neomycin, and polymyxin offer hope of additional cures.

Reports thus far on the use of these newer antibiotics in subacute bacterial endocarditis have been few, for penicillin is still the drug of choice in this disease and it is only when it fails or the causative agent is one more likely to yield to the others that they have been used. A search of the literature reveals only ten cases of subacute bacterial endocarditis which have been treated with Chloromycetin, of which four patients recovered.

The earliest report of its use in subacute bacterial endocarditis is that of de Swiet,[2] in 1949, who used Chloromycetin unsuccessfully in a fatal case due to *Salmonella typhimurium*. However, at post mortem, smears and cultures of the vegetations on the mitral valve revealed no bacteria. In May, 1950, Astler and Morgan[3] reported a case of subacute bacterial endocarditis caused by *Streptococcus fecalis* which was resistant to penicillin and therefore was treated with aureomycin and later with Chloromycetin. This patient improved clinically, but the blood culture remained positive. The third failure with Chloromycetin was reported by Monnet and associates[4] in 1950. Here also the causative agent was *Streptococcus fecalis* and it was penicillin resistant. However, only about 6 Gm. of Chloromycetin were administered.

The first successful use of Chloromycetin in subacute bacterial endocarditis was reported by Curtin[5] in 1950. The patient was a 23-year-old white woman in her eighth month of gestation. *Streptococcus viridans* was cultured from the blood. Penicillin was given for sixty-five days, during which time the blood culture became sterile. Eight days after the penicillin was discontinued, however,

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the blood culture was found to be positive again. The patient was then given Chloromycetin for twenty-two days, during which period she received a total of 68 Gm. Recovery was complete and there was no further recurrence after Chloromycetin therapy was discontinued.

Kane and Finn,[6] in 1951, reported the results of treating eleven cases of subacute bacterial endocarditis with aureomycin and Chloromycetin. In five cases Chloromycetin was the prime drug or followed the unsuccessful use of other antibiotics. Two of these cases recovered. In one, *Streptococcus viridans* was the causative agent and recovery followed the administration of 140 Gm. of Chloromycetin over a period of thirty-five days. In the other, no organism was cultured, but clinically the patient was considered to have bacterial endocarditis, which responded to 87 Gm. of Chloromycetin over a period of twenty-nine days after penicillin and aureomycin had failed. Of the three Chloromycetin-treated failures, two were caused by *Streptococcus viridans* and one by *Staphylococcus aureus*. Kane and Finn believed that penicillin was still the antibiotic of choice in the therapy of subacute bacterial endocarditis due to *Str. viridans* and *Str. fecalis*. They also observed that aureomycin and Chloromycetin were not successful when penicillin had previously failed, but penicillin was curative when aureomycin and Chloromycetin did not control the infection.

The fourth successful Chloromycetin-treated case of subacute bacterial endocarditis was reported by Gray and Stokes[7] in 1951. The patient, a 27-year-old woman, infected with *Actinomyces muris*, recovered on treatment with 65 Gm. of Chloromycetin over a period of twenty-eight days.

The fifth successful Chloromycetin-treated case of subacute bacterial endocarditis is reported herein.

CASE REPORT

A 21-year-old Puerto Rican man was admitted to the City Hospital, Medical Service of Dr. H. E. Marks, on Aug. 7, 1951, complaining of easy fatigability and an increase in exertional dyspnea. The patient stated that he had been born a "blue baby" and that he had always had some degree of dyspnea on exertion. Nevertheless, he had been able to complete eight years of school with little limitation of physical activity. For the past six months, however, he had noticed that ordinary walking caused undue fatigue and dyspnea. There was no peripheral edema, palpitation, vertigo, or paroxysmal nocturnal dyspnea.

Physical examination revealed a moderately well-developed, well-nourished man with dusky cyanosis of the lips and nail beds and clubbing of the fingers and toes, which were long and tapering. The significant findings were limited to the cardiovascular system. The heart was enlarged to percussion. There was a systolic thrust in the sixth intercostal space 4.5 cm. from the left border of the sternum. A loud, harsh systolic murmur was heard over the entire precordium, loudest in the sixth left intercostal space and in the second right intercostal space. This murmur was transmitted upward to the neck vessels. The pulse rate was 52 per minute and regular. The blood pressure was 108/70 mm. Hg in the left arm and 110/70 mm. Hg in the right arm.

Laboratory studies showed the urine to be within normal limits. The red blood cells numbered 7.66 million with 22.5 Gm. of hemoglobin (Sahli). There were 8,300 white blood cells, with 54 polys, 33 lymphocytes, 8 monocytes, and 3 eosinophils on differential smear. The hematocrit was 75 c.c. per 100 c.c. of blood. The electrocardiogram demonstrated a marked right axis deviation and a vertical heart with clockwise rotation. The P-R interval was 0.16 second. There was prominence of the left ventricular curve, blunting and elevation of the apex of the heart on the roentgenogram. The cardiothoracic ratio was 12.5/25 cm. The left auricle, great vessels, and the lung fields were within normal limits. The venous pressure was 110 mm. of water. The circulation time was: arm-to-tongue, 7 seconds; arm-to-lung, 4 seconds.

Diagnosis was congenital heart disease, probably a tetralogy of Fallot.

Course.—On the tenth hospital day, the patient complained of general malaise and had a temperature of 102°F. There was no change in the physical findings at this time. A blood culture was taken. In the afternoon, the temperature rose to 104°F. Because of the patient's cardiac status, therapy was started with penicillin 300,000 units two times a day and Gantrisin 4 Gm. initially and 1 Gm. every four hours thereafter. The temperature dropped promptly and it did not rise above 99.4°F. for the next seven days.

On August 23, the seventeenth hospital day, the blood culture was reported to show a growth of *Staph. aureus* most sensitive to penicillin, very sensitive to terramycin and Chloromycetin, and moderately sensitive to aureomycin, bacitracin, and dihydrostreptomycin. The penicillin dosage was increased to 1.2 million units daily and Gantrisin was discontinued.

For the next seventeen days, the patient continued to have a daily temperature elevation varying from 99.2 to 100.2°F. On the evening of September 10, the thirty-fifth hospital day, the temperature rose to 104.6°F.; on the following morning (the thirty-sixth hospital day), the patient was found in a semistuporous condition. Aphasia, a right facial palsy, and a right hemiplegia were present. There were numerous petechial hemorrhages under the nails of both hands. The deep tendon reflexes were exaggerated and there was a positive Babinski present on the right. The temperature was 99.6°F. A blood culture was taken, which was later reported as negative. The penicillin dosage was increased to one million units every three hours. This dosage was continued for ten days, during which time the patient continued to have a daily temperature as high as 103°F.

On September 19, the forty-fourth hospital day, the patient complained of pain at the end of his penis and passed approximately 100 c.c. of dark red blood per urethra. The blood urea nitrogen was 31 mg. per cent. On the afternoon of that same day, it was noted that the right arm was considerably cooler than the left. The blood pressure was 90/70 mm. Hg in the left arm and unobtainable in the right arm. No oscillometric readings were obtainable in the right forearm. In view of the repeated emboli and the continuation of the elevated temperature, it was felt that the penicillin was of no avail and therefore it was discontinued in spite of the negative blood culture. On this same day, the patient was started on Chloromycetin 1.0 Gm. every six hours.

On October 9, the patient complained of pain and tenderness in the toes of the right foot. All pulsations up to and including the femoral artery were absent in the right lower extremity. The right foot was cooler than the left, but there was no change in color. He was given 25 mg. of Priscoline and 2 grains of papavarine every four hours for ten days. The condition of the leg remained unchanged. On October 21, Dicumarol therapy was instituted. The prothrombin time was maintained between 25 and 35 seconds with a standard of 15 seconds plus or minus one. On October 29, the Dicumarol was discontinued.

On October 24 (the thirty-sixth day of Chloromycetin therapy), the patient's temperature became normal, and there has been no temperature elevation since that day. The Chloromycetin was discontinued on November 6. Blood cultures have been repeatedly negative; the last one reported was taken on Dec. 6, 1951. When seen on Dec. 18, 1951, the patient was still well.

The patient received a total of 97.5 million units of penicillin and 186.5 Gm. of Chloromycetin. At present he is receiving daily physiotherapy plus speech therapy awaiting final disposition as a custodial problem.

COMMENT

The diagnosis of the tetralogy of Fallot was based on the history of cyanosis from birth, long tapering fingers, frail body structure, clubbing of fingers and toes, polycythemia, roentgenographic appearance of the heart, cardiac murmur, and right axis deviation on the electrocardiogram. On the tenth hospital day, the patient developed a fever. Blood culture showed the presence of *Staph. aureus* which in vitro was most sensitive to penicillin and less sensitive to Chloromycetin.

Penicillin and Gantrisin therapy were instituted. The temperature fell to normal, but rose again and remained elevated.

On the thirty-sixth hospital day, an embolus to the brain occurred. Blood culture was sterile at this time. The sudden occurrence of bloody urine and a cooler right arm as compared with the left on the forty-fourth hospital day indicated emboli to the kidney and right arm, respectively. The continued activity of the disease process manifested by repeated emboli and the continuous fever pointed to the ineffectiveness of penicillin in spite of the marked sensitivity of the causative agent in in-vitro studies and negative blood cultures. Accordingly, Chloromycetin replaced the penicillin.

Soon after the institution of Chloromycetin, the temperature fell to lower levels, and on the thirty-sixth day (seventy-ninth hospital day) of Chloromycetin therapy, it became normal. An embolus to the right lower extremity occurred on the sixty-fourth hospital day. Chloromycetin treatment was discontinued on the ninety-second hospital day. In all, the patient received 97.5 million units of penicillin and 186.5 Gm. of Chloromycetin for periods of thirty-five and forty-nine days, respectively. The blood cultures were repeatedly negative after the initial positive culture.

SUMMARY

A patient with a tetralogy of Fallot developed subacute bacterial endocarditis manifested by elevated temperature, blood culture of *Staph. aureus* and emboli to the brain, kidneys, right lower, and right upper extremities. The responsible organism, *Staph. aureus*, was most sensitive to penicillin and moderately so to Chloromycetin as shown in in-vitro tests. Penicillin at first seemed to control the infection, but then was of no avail. The disease continued its activity as evident from repeated emboli and continuous fever. Chloromycetin in a total dosage of 186.5 Gm. over a period of forty-nine days controlled the infection and resulted in recovery. Six weeks following the discontinuance of therapy, the patient was well except for his initial complaint and the results of the emboli. This is the fifth such recovery reported in the literature after the use of Chloromycetin.

Thanks are due to Dr. Henry E. Marks for permission to report this case.

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THE COMBINED USE OF AUREOMYCIN AND TERRAMYCIN IN THE TREATMENT OF SUBACUTE ENTEROCOCCAL ENDOCARDITIS

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THE FOLLOWING is the case report of enterococcal subacute bacterial endocarditis which responded to treatment with combined oral Terramycin and oral aureomycin, after having been resistant to penicillin, streptomycin, and aureomycin. The course strongly suggested that Terramycin was primarily responsible for the cure. The organism was identified as a member of the enterococcal group, but the species was not established because of a technical error in the laboratory. It was thought that *Streptococcus faecalis* was the probable identity of the organism, although it was possible that it was one of the other members of the enterococcal group. A review of the literature has failed to reveal any other case report of cure of enterococcal endocarditis with Terramycin. Blake and associates[1] have described a case of subacute endocarditis due to *Str. faecalis* in which there was a good initial response to Terramycin, but relapse occurred six days after treatment was discontinued.

CASE REPORT

The patient, a 28-year-old white married woman, was admitted to the United States Air Force Hospital, March Air Force Base, Calif., on March 16, 1951, because of the onset of labor at the end of the thirty-seventh week of her first pregnancy.

Her past history was significant in that she had had acute rheumatic fever at the age of 5 years, following which she was kept at rest for three and one-half years. Although subsequently told by several physicians that she had a heart murmur, the patient did not develop any evidence of cardiac failure. The rest of her past history was noncontributory.

Her illness apparently began in December, 1950, when she developed fever, headache, and anorexia, which was diagnosed as "flu" and treated with bed rest and a single injection of penicillin (amount and type unknown). A week later she noted tender purple lesions on the palms, soles, finger tips, and pads of the toes; shortly thereafter a more generalized, erythematous, pruritic eruption appeared on the trunk and abdomen. She was told that this was a penicillin eruption. About two weeks later the patient experienced muscular soreness in the shoulders, buttocks, and legs. No joint involvement was described. During the ensuing months the patient suffered recurrent bouts of similar muscle pain, as well as the erythematous rash and tender dusky macules. During this period she was able to be up and about, cooking and performing her household duties. On March 1, 1951, she awakened with numbness and paralysis of the left lower arm from the elbow to the finger tips. Complete paralysis lasted only about forty-eight hours. Some seven days after the involvement of the left upper extremity, a similar hypesthesia and paresis occurred in the distribution of the right ulnar nerve. This also resolved spontaneously. On March 16, 1951, the patient gave birth to a viable premature infant of 37 weeks' gestation.

Physical examination at the time of hospital admission revealed the following: The temperature was 99°F., pulse 100, respiration 24, and blood pressure 110/70 mm. Hg. The patient appeared pallid, underweight, and chronically ill; she complained only of labor pains. Examination of the skin disclosed scattered purplish tender macules, about 5 mm. in diameter. Several splinter hemorrhages were noted under the finger nails, along with a single petechial hemorrhage in the

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right bulbar conjunctiva. The heart was not enlarged to percussion. A harsh, Grade III systolic murmur was heard at the cardiac apex. No diastolic murmur could be heard. The pulmonic second sound was accentuated. There was no evidence of congestive failure. The spleen was not palpable, although there was tenderness in the left subcostal area. The uterine fundus extended to a level 4 cm. below the ziphoid.

Laboratory Findings.—Hemoglobin was 10 Gm. per 100 c.c.; the red blood count was 2,600,000; the white blood count was 10,450; 78 per cent neutrophils, 21 per cent lymphocytes, 1 per cent monocytes. Catheterized urine showed one plus albumin and many red blood cells per high-power field. Sedimentation rate was 32 mm. after one hour, bleeding time 2 minutes and 10 seconds, clotting time 5 minutes and 20 seconds, and prothrombin concentration 80 per cent. Electrocardiogram was normal. Numerous blood cultures were taken, and on the fourteenth hospital day an enterococcus was grown. Its species identity was not established because of laboratory error. The qualitative sensitivity pattern revealed sensitivity to Terramycin and aureomycin. There was resistance to sulfanilamide, sulfadiazine, sulfamerazine, sulfathiazole, penicillin, and streptomycin.

Following her admission the patient ran a low-grade febrile course with daily temperature spikes reaching as high as 101.8°F. There was almost daily evidence of new emboli to the skin, conjunctivae, knees, spleen, and kidneys. She became weaker, more anemic, and continued to lose weight. On the fourth hospital day one million units of aqueous penicillin G given intramuscularly was started at two-hour intervals. Despite this treatment the fever and embolic phenomena persisted. Streptomycin in doses of 0.5 Gm. intramuscularly every six hours was added to the penicillin therapy on the twenty-first hospital day. Fever and inanition continued unchanged on the combined penicillin-streptomycin regimen. On the thirtieth day after admission, oral aureomycin (0.5 Gm. every six hours) was begun in conjunction with the other antibiotics. By the thirty-eighth day it was apparent that the organism was highly resistant to all drugs given, since the patient's downhill course continued unabated. Because the in vitro studies had shown that the enterococcus was markedly sensitive to Terramycin, it was decided to administer the latter drug. The penicillin and streptomycin were discontinued. Aureomycin, although it had been totally without effect during the previous nine days, was continued. This was thought justified since in vitro sensitivity to the drug had been demonstrated. On the thirty-ninth hospital day, Terramycin was given by mouth in doses of 0.5 Gm. every six hours, along with the previous dose of aureomycin.

Within thirty-six hours after the initial dose of Terramycin, remarkable improvement was witnessed. The fever disappeared for the first time in six weeks and the patient noted considerable subjective relief. The embolic phenomena, which had been continuing at intervals throughout the penicillin-streptomycin-aureomycin regimen, ceased. The anemia, which likewise had been progressive and had required numerous transfusions, began to improve. During the ensuing month the patient remained asymptomatic, except for one temperature elevation to 99.2°F. (Fig. 1). Because of the apparent cure, Terramycin and aureomycin were discontinued on the sixty-fourth day of hospitalization. Three days later the patient suddenly was seized by a Jacksonian convulsion commencing with twitching movements in the fourth and fifth fingers of her right hand associated with similar tonic movements of the right side of face. Intravenous nicotinic acid and oxygen were given immediately, and the convulsion ceased after three minutes. No neurologic sequelae were observed. Since it appeared that the subject had suffered a cerebral embolus, possibly septic, Terramycin therapy in the original dosage was reinstituted. Aureomycin, this time, was omitted.

During the days which followed, the patient continued to have identical focal epileptic seizures. Although the spinal fluid examination was negative, the possibility of brain abscess formation seemed likely, and the dosage of Terramycin was increased to 4 Gm. per day. Phenobarbital was given to suppress the irritable focus. Thereafter, the patient remained asymptomatic. The red blood count and hemoglobin level rose to normal levels; the sedimentation rate remained under 20 mm.

On the one hundred-seventh hospital day the patient was sent home for additional convalescence, feeling quite well except for understandable asthenia after her prolonged illness. Because

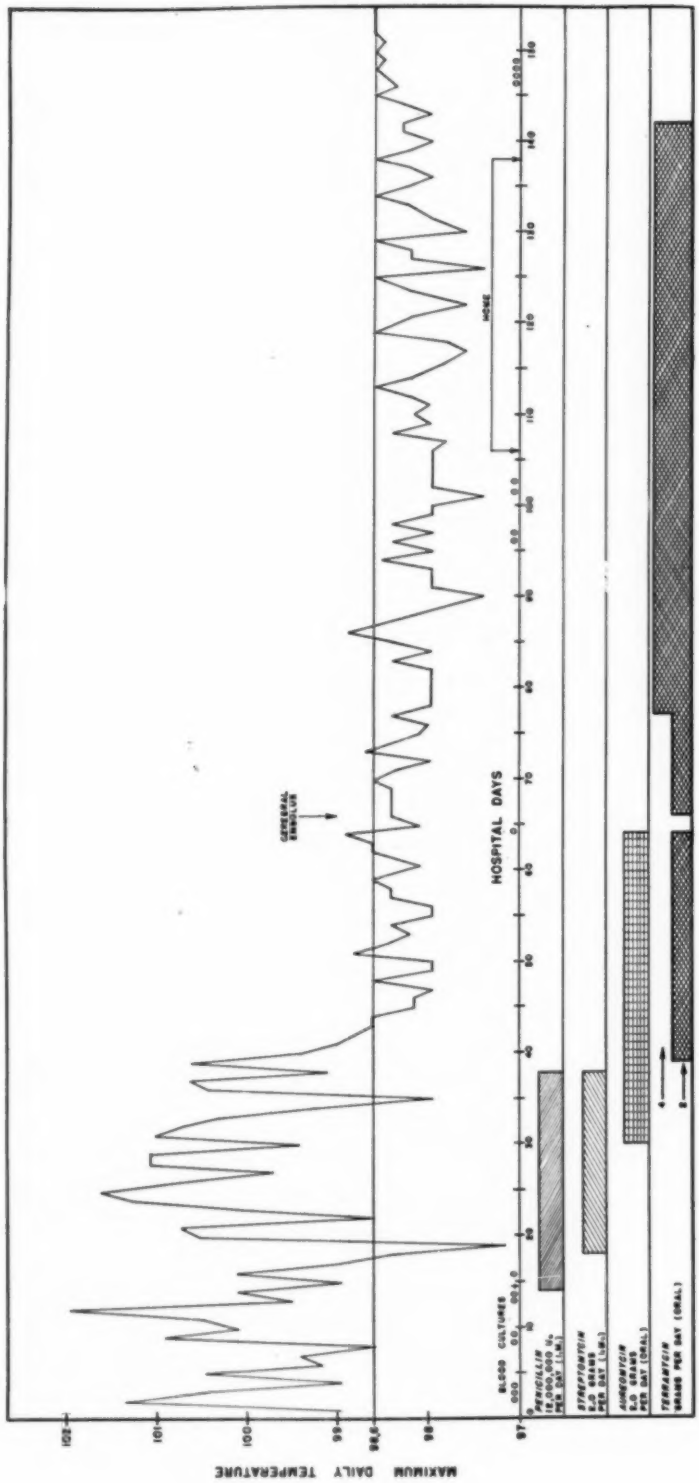
MAXIMUM DAILY TEMPERATURE
HOSPITAL DAYS
GENERAL ANESTHESIA
HOME
BLOOD CULTURES
PENICILLIN 10,000,000 U. PER DAY (I.M.)
STREPTOMYCIN 2.0 GRAMS PER DAY (I.M.)
AUREOMYCIN 2.0 GRAMS PER DAY (ORAL)
TERRAMYCIN 1 GRAMS PER DAY (ORAL)

Fig. 1.

of the danger of relapse, she was given Terramycin (1.0 Gm. every six hours) during this period. For the month which followed she was limited to sedentary activity. A record was maintained of her temperature at six-hour intervals, and this remained normal. At the end of a month at home she was readmitted to the hospital for further study prior to cessation of the Terramycin. She was found to be quite well. Twenty pounds had been gained, her blood count was normal, and, although the mitral systolic murmur was considerably louder and harsher than it had been on admission, there was no evidence of cardiac failure. Blood cultures were sterile. The Terramycin was discontinued and there was no clinical or bacteriologic evidence of relapse thereafter. The patient was followed in the outpatient clinic for four additional months and during this period she has remained well.

DISCUSSION

Unfortunately, the exact species of organism concerned here remains unknown. All that can be stated definitely is that it was a member of the enterococcus group. The onset during pregnancy and the clinical course which ensued were both consistent with the usual features of enterococcal endocarditis.[2-4] On the basis of statistics alone one might implicate *Str. faecalis*; however, one must also consider the less common members of the enterococcus family.

The initial use of penicillin was based on the presumption that this was a *Str. viridans* infection. When bacterial identification revealed an enterococcus, the combined use of penicillin and streptomycin, as suggested by Robbins and Tompsett,[2] was employed. As noted above, there was no discernible effect from this combined therapy. Because of the failure to respond to these two antibiotics, aureomycin, to which there was in vitro sensitivity, was added. Finally, penicillin and streptomycin were discontinued, and Terramycin was given along with the aureomycin. As cure occurred during the use of the two latter drugs, it is impossible to state unequivocally whether the response was due to either one singly or to their simultaneous use. The striking change observed after the administration of Terramycin suggested that this agent was primarily responsible for the cure. This impression was strengthened by the previous failure of the aureomycin. Moreover, during the final seventy-eight days of treatment only Terramycin was given.

The choice of an antibiotic in the treatment of enterococcal endocarditis has remained an unsettled issue. Each new drug, as it becomes available for clinical trial, has been used with varying success. Penicillin alone has usually resulted solely in temporary control of the infection, although there are a few recorded instances of cure.[5,6] The response to streptomycin has been disappointing.[7] Concurrent administration of penicillin and streptomycin has produced results superior to the use of these agents singly.[2] Recently Long and associates[8] have reported the successful use of oral aureomycin in two cases. However, Harvey, Mirick, and Schaub in employing aureomycin have met failure as often as success.[9] As mentioned previously, the only other recorded instance of the use of Terramycin[1] was a case in which prompt relapse occurred after an excellent early response.

SUMMARY

A case of enterococcal subacute endocarditis is reported in which cure was effected by the combined use of Terramycin and aureomycin, after failure with triple antibiotic treatment with penicillin, streptomycin, and aureomycin. Although Terramycin was initially administered with aureomycin, the clinical course strongly suggested that the response was primarily due to Terramycin.

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Review of Recent Advances

THE ELECTROCARDIOGRAPHIC EXERCISE TEST

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A RELIABLE diagnosis of coronary artery disease is often difficult. It is not possible in many instances to discover any clinical evidence of stenosis of the coronary ostium in syphilitic aortitis or arteriosclerotic narrowing of a coronary artery. One can be reasonably sure of the diagnosis if the patient relates a typical history of angina pectoris or the electrocardiogram shows a myocardial infarction. Frequently in clinical practice the history and findings are atypical; also in insurance problems and in examinations for employment the history is unreliable. Then the diagnosis is uncertain and there arises a pressing need for objective evidence of coronary artery disease.

Twenty years ago, almost simultaneously, two tests were recommended for this purpose: the anoxemia test and the exercise test. The exercise test, which is the more practicable, is the subject of this review.

A critical evaluation of the exercise test is in order because of the great confusion which exists concerning its technique and interpretation. Variations in the method of exercise produce variable effects in the electrocardiogram. Furthermore, too much exercise may seriously harm the patient while too little may fail to reveal the inadequacy of the coronary blood flow. The interpretation of the electrocardiogram likewise varies tremendously. Each investigator has set up his own range of normalcy for the changes which appear following exercise. This has confused the practicing physician. Many do not fully appreciate the changes which normally result from exercise. Hence there is a tendency to consider these normal changes as abnormal, and to diagnose coronary disease to the detriment of the patient. Many published illustrations of allegedly positive exercise tests are well within the range of normal.

In the present study an attempt will be made to correlate the multitude of reports on the test with the known facts and likely theories of the physiology of the coronary circulation and the electrocardiogram. Thereby it is hoped that the differences in technique and interpretation of the test will be reconciled to a great extent. This should aid in the establishment of a universally accepted method of performing and interpreting the test. Furthermore, an attempt will be made to emphasize those aspects of the test which require further investigation.

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DEFINITION

The exercise test is an electrocardiographic test for the adequacy of the coronary blood supply when the demand for the latter is increased by exercise. If the supply is inadequate the electrocardiogram often shows diagnostic abnormalities.

The often-used phrase "exercise tolerance test" is inaccurate because the ability of the patient to perform exercise is not being tested. Nor is it a test for angina pectoris since it is not intended to induce anginal pain, though this often happens.

HISTORICAL REMARKS

In 1908 Einthoven investigated the effect of physical exertion on the electrocardiogram.[15] He described an increase in the height of the P and T waves and a depression of the P-R segment; he also noted that a negative T in Lead III became positive. Bousfield in 1918[6] and Cowan and Ritchie in 1922[10] described the changes appearing during a spontaneous attack of angina pectoris. In 1928 Feil and Siegel[18] described additional instances of electrocardiographic changes during spontaneous anginal attacks and also during attacks induced by the exertion of coming to the laboratory. In 1931 Wood, Wolferth, and Livezey[82] investigated the changes seen in normal subjects and in patients with angina pectoris after exercise consisting of climbing stairs. These authors concluded that ". . . the use of our electrocardiographic procedure to diagnose angina pectoris is not recommended. Although there were no untoward occurrences in our series of cases, it is admittedly dangerous to induce anginal attacks indiscriminately" and ". . . clinical observations are more likely to be significant from a diagnostic standpoint than electrocardiographic phenomena."

In 1932 Goldhammer and Scherf[29] found electrocardiographic changes in eleven of twenty patients with angina pectoris after exercise; they recommended the use of moderate exertion as a diagnostic test when the diagnosis was otherwise doubtful. In 1933, on the basis of a greater experience, the same authors recommended the exercise test to determine the adequacy of the coronary circulation for the early diagnosis of angina pectoris.[67,68] Further results were reported in the following years.[21,62] Soon many others reported their experiences with the test.[29,33,50,71] In 1938 the first monograph on the exercise and anoxemia test appeared.[39] A modification of the test, which is known as the two-step test, was published by Master and associates.[46]

NORMAL AND ABNORMAL CHANGES IN ELECTROCARDIOGRAM AFTER EXERCISE. CRITERIA FOR NEGATIVE AND POSITIVE EXERCISE TEST

The early investigators often registered only one lead; as a result their reports are difficult to evaluate (see Kahn[32] for early literature). Later more adequate methods were used. Enough leads were employed to permit an estimation of the changes of the vectors of the different complexes; however, the results were rarely correlated with the amount and type of exercise and with the degree of training (or physical fitness) of the subjects. Few reported the phasic changes

that appeared during, immediately after, and for a variable period following exercise.

The literature on this subject is so vast that a complete discussion is impossible in the framework of this review. A knowledge of the normal changes and their dependence on the various conditions mentioned above is important for the recognition and evaluation of the abnormal changes seen in coronary artery disease. Furthermore, such knowledge is a prerequisite for a general agreement as to how the test should be done and the tracings interpreted.

Exercise causes the *P wave* to become larger, mostly in Leads II and III; a negative P in Lead III may become positive. These changes are an expression of the tendency of the P vector to become more vertical. During exercise the diaphragm descends and for a while remains in a more inspiratory position; thereby, the heart becomes more vertical.[52] It is unknown whether an increase in the magnitude of the P vector could be caused by the increased potential accompanying increased mechanical effort. To investigate this, a study of the changes of the auricular spatial vector loop after exercise might be instructive.

The *Ta wave* becomes more pronounced after exercise.[67] This is only partly due to the increased size of the P wave. According to the current theory of the Ta wave, the area subtended by the P wave (auricular activation) is equal in size and opposite in polarity to the area of the Ta wave (auricular recovery). An increase of P is therefore accompanied by an increase of Ta. However, the chief reason for the more pronounced Ta wave in the test is the tachycardia following exercise. As the heart rate increases, the duration of the monophasic action current of the myocardial elements decreases. The decrease of the refractory period and of the Q-T interval are well-known manifestations of this principle. The shortening of the monophasic action current involves chiefly the recovery phase, which inscribes the Ta wave. As the Ta wave shortens, it must deepen in order to maintain an area equal and opposite to that of the P wave. Both vagus stimulation and acetylcholine make the Ta wave more pronounced[71] in accord with the explanation just given. It is well known that they shorten the monophasic action current of the auricular myocardium.*

It is generally appreciated that auricular infarction distorts the Ta wave by means of injury currents.[1,37,38,76] While this has not yet been described as a transitory manifestation after exercise, its probability is so great that a search for it should be instituted. Deviations of the Ta wave due to injury currents can only be diagnosed when the Ta wave deviates in the same direction as the P wave. When P is positive, Ta should be elevated; when P is negative, Ta should be depressed. Pathologic displacements of the Ta wave in a direction opposite

*It is not amiss to discuss briefly the application of the above theory to the understanding of the large saw-toothed auricular waves seen in auricular flutter. These have long been regarded as an expression of the circus movement of the activation wave in the auricle. The entire auricular complex was considered a manifestation of the activation phase. Recent experimental evidence indicates that auricular flutter is caused by rapid ectopic stimulus formation.[70] Moreover, flutter waves contain both activation and recovery components, corresponding to the P and Ta waves,[55] and tachycardia may cause the Ta waves to enlarge and become as symmetrical as the P wave. This has been explained by postulating myocardial damage[55] or by conduction with a decrement.[60] This explanation is unnecessary, for tachycardia alone, by shortening the monophasic action current, can account for the large Ta waves.

to the P wave occur after exercise, but they cannot be differentiated from the normal deviations of the Ta wave.

The Ta wave lasts well beyond the end of the QRS complex even when the duration of P-Ta period is shortened by tachycardia. Therefore it can cause the ventricular S-T segment to deviate. In the literature are many instances where an S-T deviation caused by a Ta wave has been erroneously diagnosed as pathologic. In order to avoid this mistake one should, when measuring the level of the S-T segment, use the junction of the P-R segment with the QRS complex as a reference level[29] as recommended by the American Heart Association. Sometimes even this is not satisfactory and one may extend a sloping P-R segment into the S-T segment in order to estimate the amount of deviation due to the Ta wave. The use of Lead V_5 also is very helpful, for here the P-Ta complex is usually small and the true S-T deviations are large.

A sinus tachycardia in a patient without evidence of heart disease is shown in Fig. 1. The advantage of using the position of the base line at the beginning of the QRS complex as a reference level for the S-T segment is evident. In many publications this is not done and an S-T segment like that in Fig. 1 is diagnosed as abnormally depressed.

After exercise the *P-R interval* normally may shorten by 0.01 to 0.02 second. Occasionally a slight lengthening of the same degree is seen. This variable response is understandable since atrioventricular conduction time depends on such antagonistic factors as changes in the tonus of the vagus and sympathetic systems on the one hand and the fatigue resulting from the increased rate on the other. In the presence of partial atrioventricular block, exercise may lead to a higher degree of block.[66]

The *QRS complex* often shows changes consistent with a mild deviation of its vector to the right, presumably due to the descent of the diaphragm. The R in Lead I is diminished, the S increased; in Lead III the R is increased. Occasionally all QRS complexes become larger. The width of the QRS complex diminishes slightly because of changes in the sympathetic tonus; this is ascertainable only by high-speed recordings. The effect of exercise on the magnitude, form, irregularities, and position of the spatial vector loops of the QRS complex are not known.

Any definite widening of the QRS complex after exercise is pathologic.[78] The appearance of bundle branch block (usually right bundle branch block) has been observed in attacks of angina pectoris[6]; the same has been seen repeatedly after exercise[23,34] in patients with coronary artery disease. One should realize, however, that any increase of rate may transform normal intraventricular conduction into bundle branch block without coronary sclerosis necessarily being present.

The *S-T segment* often shows pronounced deviations following exercise in the healthy individual. It is usually depressed in the standard leads, in aV_L, aV_F, and V_5, V_6, but is elevated in aV_R. In general, after exercise the S-T vector tends to become oppositely directed to the QRS vector. Similar S-T deviations appear following exercise of patients with coronary disease, only the amount of deviation is more marked. In fact, the S-T changes are the most

important criteria for the clinical interpretation of the exercise test. Unfortunately the differentiation between normal and abnormal S-T variations is often difficult. The clinical interpretation of the test may be aided by an understanding of the theoretical background for the S-T changes seen following exercise.

The currently accepted theory of the S-T segment and T waves (electrical recovery process of the ventricles) can account for many changes seen after exertion. It is assumed that the inner layers of the myocardium recover slower

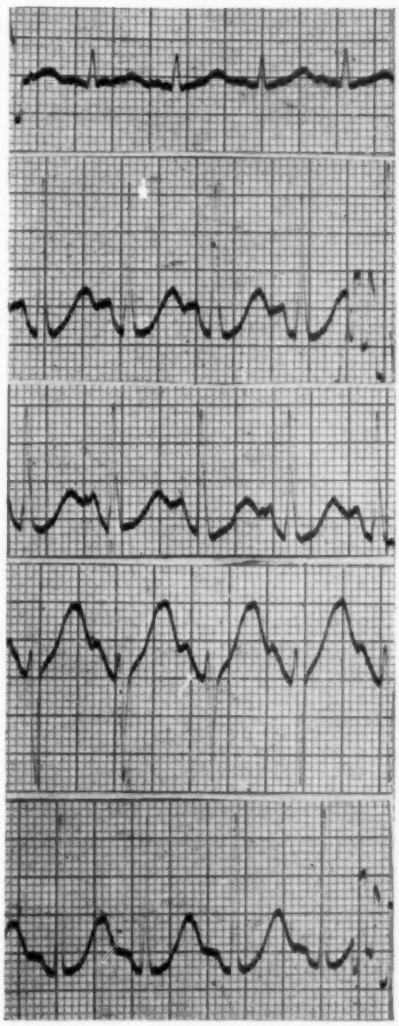


Fig. 1.—Sinus tachycardia in a 48-year-old woman with Jacksonian epilepsy; there was no evidence of cardiovascular disease.

than the outer layers. The latter, though activated later, recover earlier. This produces an ST-T vector which points to the outer layers and is approximately parallel to the QRS vector. The difference in the *rates* of recovery of the various regions is called the ventricular gradient and can be represented as a vector force.[2] The normal gradient is directed approximately parallel to the QRS vector. In the electrocardiogram a reduction of the gradient is manifested by a depression

of the S-T segment or flattening to inversion of the T waves in those leads which display an upright QRS complex. When the gradient is reduced to zero all parts of the myocardium recover with equal speed. The pathway of recovery is identical with that of activation. Thereby the area of S-T and T becomes equal and opposite to the QRS. This is normal for the auricular myocardium but not for the ventricular.

An increase of the heart rate normally decreases the gradient.[2] Simple tachycardia in a normal individual can thereby result in a pronounced S-T deviation.[2,75] The shortening of the monophasic action current by tachycardia appears to affect the inner layers more than the outer ones. While with a normal rate, the inner layers have a longer lasting action current than the outer ones, with an increased heart rate, the speed of recovery of the inner layers tends to become equal to that of the outer layers. This in turn signifies a decreased gradient. Exercise, by the almost invariable tachycardia that ensues, decreases the gradient. If the increase in rate following exercise could be prevented, the gradient should not decrease.

There is some factor in exercise which tends to increase the gradient. This second factor is deduced from the observations of both Ashman[2] and Sjöstrand[75] that the tachycardia of exercise is accompanied by a smaller decrease of the gradient than a simple tachycardia of the same rate elicited by other means. One might conceive this action as a tendency to delay the recovery process of the inner layers by the increased mechanical effort of the heart inherent in exercise. Ashman suggests that it might be related to the stroke volume. It might be called the effort factor as contrasted with the tachycardia factor. The effort factor may be one of the causes of the increased height of the T waves following exertion (See. below).

Another result of tachycardia, apart from the gradient effect, is the accentuation of S-T segment and the T wave. This was explained above in connection with the Ta wave. When the monophasic action current is shortened by the tachycardia, the shortening affects chiefly the recovery process. This results in a shorter Q-T interval. In order to maintain the same area as before (the gradient remaining constant for the moment), the ST-T complex must develop a greater amplitude. If originally positive it becomes even more positive; if negative it becomes more negative. This action, plus the decreased gradient, accounts for the marked deviations of the S-T segment in simple tachycardia. It also contributes to the increased height of the T wave following exercise. The latter could therefore be explained by either the increased gradient due to the effort factor or by the ST-T shortening effect of tachycardia. An investigation of the rate that prevails when marked peaking of the T waves appears following exercise might contribute additional information.

Posture also exerts an influence on the gradient and ST-T complex.[2,47,72,75] Head-down position appears to increase the gradient, resulting in elevation of the S-T segment and increase of the T wave. Standing appears to decrease the gradient; the S-T is depressed and the T wave becomes smaller or inverted in Leads II and III or even in all three standard leads. These changes are partly due to change of position of the heart, to alteration of the tonus of the autonomic

nervous system, and perhaps variations of the stroke volume. The posture factor can account for the increase of the amplitude of T when the patient lies down immediately after exercise.[75]

An increase of the sympathetic tonus connected with exercise also influences the recovery process and thereby modifies the ST-T complex. This action seems to be complex and has been insufficiently analyzed.[56]

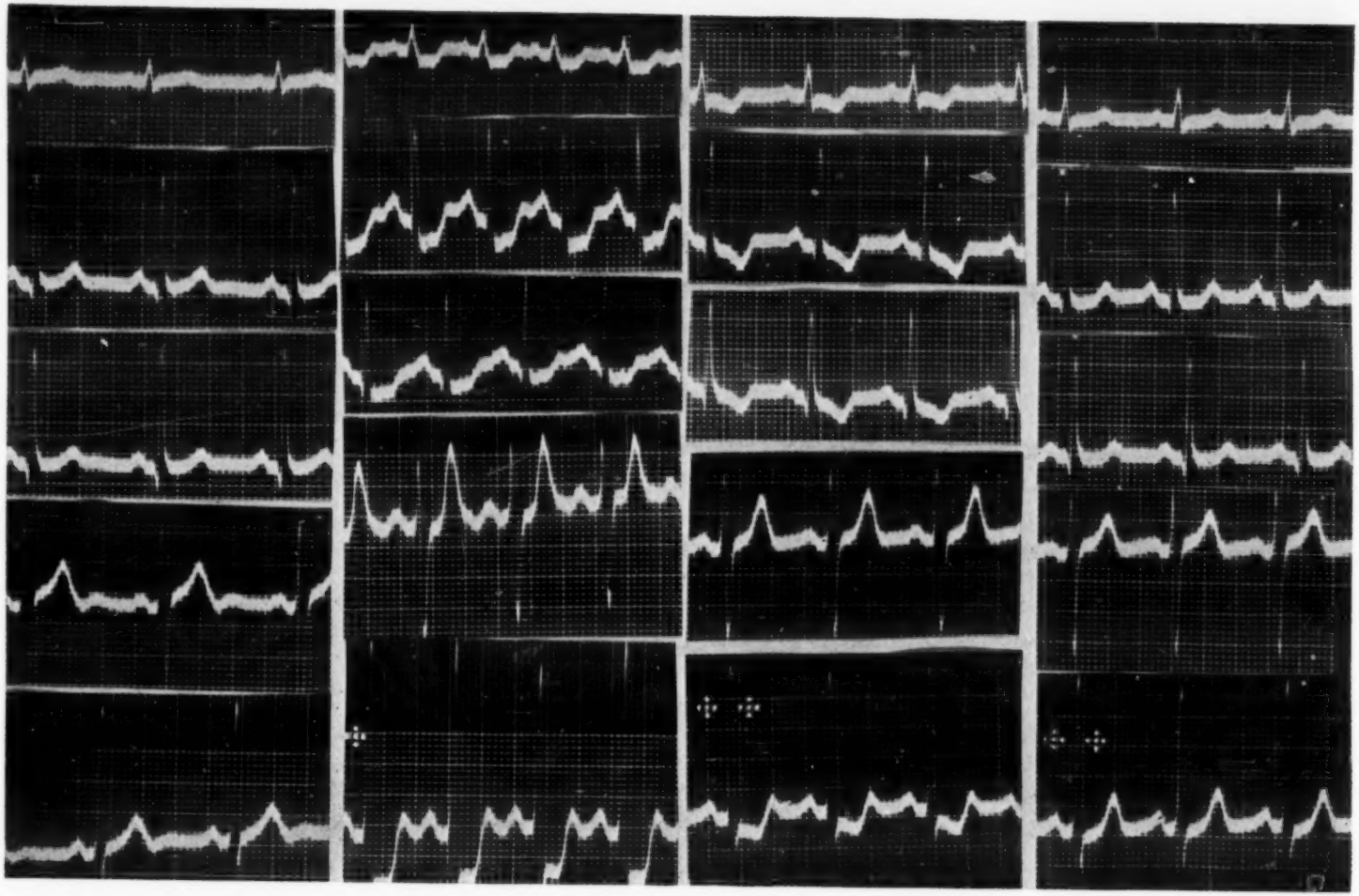
The decrease in the gradient as a result of exercise causes the ST-T vector to become oppositely directed to the mean QRS vector. Accordingly, normal subjects after exercise will show a depression of the S-T segment in leads where the QRS complex is positive; in leads where the QRS is negative the S-T segment will become elevated. When the mean QRS vector tends to deviate to the left (horizontal heart) the S-T will be depressed most in Leads I and II; when the mean QRS vector is more vertical the S-T depression will be most pronounced in Leads II and III. The junction J is also deviated in the same direction as the S-T segment.

When a patient with coronary artery disease performs exercise, the ST-T complex is influenced not only by the above-mentioned normal factors but also by an additional one, namely, inner layer ischemia. When ischemia affects the entire heart, the inner layers of the ventricular myocardium suffer earliest and most intensely. The chief action of ischemia is anoxia. Anoxia shortens the duration of the electrical recovery phase of the myocardial fiber. If the inner layers are chiefly affected, the gradient decreases. When the ischemia becomes more severe, the fibers suffer a decrease of resting potential or they fail to be activated or both. This gives rise to injury currents, which appear in the electrocardiogram as deviations of the S-T segment. The S-T vector which represents the injury current always points to the injured area. Accordingly with inner layer injury, the S-T injury current vector points from the outer to the inner layers and is more or less opposite to the mean QRS vector. Consequently, an S-T depression appears in those leads with an upright QRS complex, while in those leads with a negative QRS complex the S-T becomes elevated.

A marked depression of the S-T segment may draw the T wave down below the base line. The depression may be so marked that the S-T segment forms a horizontal line far below the base line, as in Fig. 2,*B* (obtained from a 40-year-old woman with angina on effort). In other cases the S-T segment merely sags (Fig. 2,*B*) or shows a depression with the convexity directed upward. In all the usual leads the S-T is depressed except in aV_R where it is elevated.

It is apparent that the S-T deviations due to tachycardia and those due to inner layer ischemia have similar directions. The distinction between the two is difficult. Indeed, the crucial function of the examiner in the exercise test is to recognize which S-T depression is due only to the decreased gradient of tachycardia and is therefore normal and which is due to ischemia and is therefore abnormal.

It has been stated that the distinction can be made by observing the contours of the S-T segments.[81] A normal S-T depression shows a rapid rise from J to T, while the abnormal one is flat or sagging. Obviously an important reason for the steep ascent of the normal S-T is the rapid waning of the Ta wave as the



A. *B.* *C.* *D.*

Fig. 2.—Exercise test in a patient with angina on effort. *A*, The control electrocardiogram before the exercise; *B* was obtained immediately after the exercise (climbing of two flights of stairs); *C* and *D*, respectively, the tracings obtained five and ten minutes after the exercise.

T is approached. Even with this method, nine out of 100 normal persons showed either abnormal curves or borderline records difficult to evaluate.

The only tried and proved method for distinguishing between normal and abnormal S-T deviations is an empirical one. It is based on the maximum amount of S-T deviation which can occur normally after exercise. There is, however, much disagreement concerning the upper limit of normal.

This difference of opinion is partly due to the difference in the purpose to which the test is put. If the test is used to eliminate the possibility of coronary artery disease, the normal limits will be so chosen as to exclude false negatives. However, if the test is used to establish a definite, incontestible diagnosis of coronary sclerosis, the object is to eliminate false positives and more strict criteria should be employed. In the first case the results will of necessity include some false positive tests, while in the second case it will yield some false negative tests. It has not been possible to devise a test that is consistently positive in every case of coronary artery disease. Therefore, we prefer the second approach; a positive test should be practically pathognomonic of coronary artery disease.

Any attempt to establish normal limits for the S-T deviation after exercise must include a consideration of the amount and rate of exercise, the physical training of the subject,[57] the emotional reaction to the test, and the tonus of the sympathetic nervous system. These factors influence the heart's reaction to exercise and the concomitant S-T deviation. For example, a trained athlete responds to great exertion with little or no increase of rate whereas a person with neurocirculatory asthenia will develop a tachycardia out of all proportion to the amount of exercise. If very severe exercise is performed by poorly trained persons, the heart may suffer organic injury.[7,39,44] The resulting electrocardiogram may show not only the marked tachycardia but also definitely pathologic complexes. After long-distance foot and ski races the following abnormalities have been noted, usually in those who finished in an exhausted condition: auricular fibrillation and inversion of the T waves in Leads I, II, and in apical chest leads. The combination of severe exercise with anoxia has been shown to cause abnormal S-T changes regularly.[84] The historical Marathon runner died after reaching his goal.

Many investigations which have attempted to establish a normal range are not strictly comparable because the factors just mentioned have not been uniform. (For the literature, see Kienle,[34] Klemola,[35] and Larsen.[39]) Some have had their patients climb a flight or two of stairs,[20,67,82] while others examined the electrocardiogram after ten flights of steps, after climbing mountains, and after long marches with full pack.[26] Furthermore the rate of exertion is important. Thus a lowering of the T wave was seen in 59 per cent of the cases when a given amount of work was done quickly and only in 16 per cent when done slowly.[26] It is important also to ascertain the time that elapsed between the effort and the recording because phasic variations are marked. The changes found immediately after exercise often differ decidedly from those seen later.

By correlating the results of the different investigations, one finds that the maximum normal S-T depression after moderate exercise is 1.5 to 2 mm. The

latter figure is rare and when present usually is found in the chest leads. It has already been explained how the P-R segment is used as the reference level. Moderate exercise is considered to be a climb of two flights of stairs at a moderate pace, bending the knees thirty times, or the equivalent.

It should be emphasized that 2 mm. is not universally accepted as the upper limit of normal for the S-T depression following exercise. For Twiss and Sokolow[78] the upper limit of normal is 1 mm. in Lead I, 1.5 mm. in Leads II and III, and 2 mm. in Lead IV. Mazer and Reisinger[48] consider as abnormal any depression beyond 0.75 mm. in Leads I and III, 1.5 mm. in Lead II, and 1.75 mm. in Lead CF_5. For Levan[41] the upper limit of normal is 0.75 mm. in any lead. Biorck[4] goes so far as to consider normal only those records in which the sum of the S-T deviations in the three standard leads is less than 2 mm. Finally Master and his associates[46] accept as the upper limit of normal as little as 0.5 mm. in any lead.

Sjöstrand[75] found depressions of the S-T segment in normal subjects of as much as 4 mm. during a tachycardia induced by amyl nitrite. This is not valid as a standard for the exercise test owing to the different nature of the causal factors. It is difficult to correlate the findings of Thomas[77] who noted an S-T depression of 1 mm. even before exercise. The factor of tachycardia may have been involved.

The above discussion indicates that all authors would agree that an S-T depression of more than 2 mm. after exercise is abnormal. The disagreement involves the interpretation of deviations less than 2 mm. If they are between 1.5 and 2 mm. we consider the test as probably abnormal. If it is less than 1.5 mm. we feel it should be interpreted as a negative, that is, a normal test. Admittedly there are instances where the combination of a decreased gradient due to tachycardia plus inner layer ischemia yields a depression of less than 1.5 to 2 mm. These are considered as a normal negative test and thereby constitute a group of false negative tests. They are unavoidable if one wishes to keep the exercise test reliable for the positive establishment of a diagnosis of coronary artery disease. The incidence of false negatives is not excessive, as will be indicated later. When the amount of S-T deviation is borderline the interpretation will of course be uncertain, just as it is when one must assign a significance to a Q wave whose size borders on the abnormal.

The usual pathologic response to exercise is relative ischemia of the heart as a whole, which, in turn, is expressed electrocardiographically as the pattern of inner layer injury. Sometimes the ischemia affects predominantly the region nourished by a single artery so that the pattern of local injury appears. This consists principally of an elevated S-T segment in some or all of the usual leads (except aV_R where it is depressed). Usually it is the pattern of diaphragmatic wall injury which appears temporarily.[9,14,22,34,40,54,58,63,65,67] This may be due to the fact that the leads commonly used in the exercise test (the limb leads and V_5) do not reflect anterior wall injury efficiently because they do not pick up the sagittal component of the heart vector. According to Holzmann,[28] inner layer damage in a horizontal heart may cause an elevation of the S-T segment in Lead III.

The local injury pattern seen after exercise usually lasts but a few minutes. In some cases, when a myocardial infarction had previously taken place, exercise brings back the same pattern of acute infarction temporarily.[29,65] In other instances, however, autopsy has failed to reveal the presence of an old infarction.[21] Occasionally, simple tachycardia without exertion or spontaneous anginal attacks may show a transient local injury pattern.[69]

Similar patterns have been observed in spontaneous attacks of angina pectoris, occurring at rest.[5,8,21,80]

The *T wave* changes that normally occur after exercise are caused by the same factors which affect the S-T segment. There is rotation of the heart to the right due to descent of the diaphragm, the decrease of the gradient due to tachycardia, the increase of the gradient due to effort and posture, and the ST-T shortening effect of tachycardia. The rotation to the right lowers the T wave in Leads I and V_5 and it may make an inverted T in Lead III upright.[15] A lowering of the T wave in all leads could be explained by a decreased gradient. The T in all leads sometimes shows an increase, occasionally after a transient decrease. The increase may be due to the effort and postural factors or to the ST-T shortening effect of tachycardia, or both.

Abnormal changes of the T wave after exercise can be ascribed to the marked decrease of the gradient as a result of inner layer ischemia. Any shift of the T vector after exercise, to the extent that a distinctly inverted T in any or all of Leads I, II, V_4, V_5, and V_6 is inscribed, is definitely pathologic. However, reversal of T waves in leads that are near the transitional zone of the normal T vector are of course not to be interpreted as abnormal. If the T wave becomes lower or inverted at a time when the tachycardia after exercise is diminishing, then its pathologic significance is enhanced.

About twenty minutes following the acute phase of inner layer injury with depression of the S-T segment and inversion of the T waves, very high T waves have been observed.[67] The mechanism of such late T wave changes at a time when the S-T segments are normal is not clear. This pattern may represent an aftereffect of a prolonged inner layer damage.[64]

The *U waves* are normally more pronounced after exercise. They may be absent before the exercise and appear for only a few minutes after. A reversal of the U waves after exercise is definitely abnormal.[53] Sometimes it is the only abnormal finding.[27] The normal U wave is positive in all leads except aV_R where it is negative.

The appearance of extrasystoles after exercise is definitely abnormal.[5,20,67] They are usually ventricular and multiform in type. Auricular fibrillation following exercise is not rare[24,31] if the exercise is strenuous; however, with the moderate exertion used in our tests it is rare. Paroxysmal supraventricular and ventricular tachycardia have also been observed following exercise.

PERFORMANCE OF THE TEST

There is no generally accepted method for fixing the amount of exercise. We prefer to regulate the amount of exercise according to the patient's statement as to how much exertion is required to induce symptoms and under what circum-

stances this occurs.[64,67] Others ask the patient to exercise until he is stopped by pain, dyspnea, or fatigue. At present a third method is in vogue: to eliminate personal factors; the amount of exercise is determined by the patient's age, sex, and weight.[45]

It is important to note that standardization of the amount of exercise according to sex, age, and weight does not augment the value or accuracy of the test. An examination of the physiologic basis of the exercise test will demonstrate this.

A marked stenosis of a coronary artery need not affect the flow of blood when the demand is low such as before exercise. This is due to the generally contracted state of the arterioles and the resulting high peripheral resistance.[21] When the demand begins to increase during exercise the flow also increases despite the stenosis by means of peripheral vasodilation. However, with a further increase in demand the stenosis becomes a limiting factor and the flow cannot meet the demand. This is the stage called "coronary insufficiency" which is expressed by either clinical or electrocardiographic manifestations or by both.

The object of the exercise test is to increase the demand for coronary blood flow to the point where any appreciable narrowing of the coronary arteries causes an inadequacy of blood supply. Obviously this point varies from patient to patient. There is no justification in raising the demands by a uniform amount in all subjects.[45,46]

Furthermore, even if there were a need for a uniform increment of the demand it could not be attained in the clinic with any type of exercise routine. The demand is proportional to the work of the heart. The latter depends not only on the amount and rate of exertion, but also on the training of the subject, his emotional reaction to the test, and the condition of his autonomic nervous system. The amount and rate of work can be controlled in the individual subject but the other factors cannot.

Therefore, the amount of exercise according to the patient's age, sex, and weight may be excessive and dangerous for one patient and inadequate and uninformative for another.

Another method of performing the test is to have the patient exercise until he is stopped by pain, dyspnea, or fatigue. This is based on the fact that the test has been found positive more often in those who experience pain during its performance. (See below.) Thus Twiss and Sokolow consider it ". . . imperative to elicit an attack of typical chest pain during the test." The patient should undergo ". . . the maximal effort he is able to perform."[31] However, we shall point out that there is no strict parallelism between degree of changes in the electrocardiogram and the discomfort of the patient. Patients may experience no discomfort, yet the tracings may show extensive changes. Because of the increased danger inherent in such a procedure this method should be used with extreme caution only in those patients where conservative methods of exertion have proved ineffective in provoking typical changes.

The method which we recommend has been used by one of us for twenty years and has been found to be practical, efficient, and safe.[62-64,67] From the patient's story one determines the amount of exertion needed to bring on symp-

toms, and also the amount which the patient permits himself to perform daily. The exercise prescribed for the test does not exceed the latter and approximates the former. Patients who develop pain only after severe exertion are asked to climb several flights of stairs rapidly. Those who experience pain after mild exertion are asked to climb one flight. Those who develop pain after the slightest exertion are asked to bend the knees a few times or to sit up in bed several times. If the patient states that the pain appears only on exertion following a heavy meal, the test is done after such a meal.[51,66,67] In order to avoid an excessive degree of ischemia of the heart muscle the first test is always limited to the amount of work which the patient does spontaneously during his daily routine. If the test is negative under these conditions and if the clinician is convinced of the necessity of a further test, the amount of exercise may be cautiously increased.

The actual form of exercise is unimportant. Stair-climbing, knee-bending, sitting-up exercises, and raising dumbbells exemplify some of the many types of exertion used and recommended.

Before the exercise is done, the history, physical findings, and electrocardiogram are evaluated. The test is done only if there is no lesion contraindicating exertion. One must be especially careful to register and interpret the electrocardiogram immediately before the test in order to detect an acute infarction that may have developed between the clinical examination and the test.[65]

Tracings should be done before, immediately after, and two, five, and ten minutes after the exercise. Immediately after the test the normal factors which affect the ST-T complex occasionally mask the pathologic ones. The abnormal changes may not appear during the first five or ten minutes after exercise.[61] Changes may last only for a few minutes or persist as long as forty minutes.[67]

Sometimes only a slight increase of the exertion will convert a negative test to a positive one. In other instances a repetition of the test within a few days will give a positive result, although a previous test performed under apparently identical conditions was negative.[67]

ELECTROCARDIOGRAPHIC CHANGES AFTER EXERCISE IN PATIENTS WITH CARDIAC PATHOLOGY OTHER THAN CORONARY ARTERY DISEASE

It is important to know what effect the exercise test has on other than coronary artery disease. This has been the subject of many investigations but the results are still not decisive.

Occasionally typical positive tests have been found after recovery from an infectious disease complicated by myocarditis.[35,49] Positive tests have been also observed in patients with rheumatic valvular disease complicated by angina pectoris.[67] There are no reports, as far as we know, on the effect of exercise on the electrocardiogram in congenital heart disease. However, anoxia tests have yielded a high percentage of positive tests (inner layer injury patterns) in such cases. Furthermore, in an infant with congenital heart disease but with normal coronary arteries, one of us has recorded a classical inner layer injury tracing.[61] The abnormalities persisted only for a few minutes.

In such cases the diagnosis of coronary artery disease on the basis of an exercise test is apparently not justified. Otherwise the test appears to be positive only in cases of coronary artery disease.

There are reports of positive exercise tests in emotionally unstable persons,[81] but the tracings shown do not support the conclusions. Either the effect of the Ta wave on the S-T segment has been overlooked or the upper limit of normal for the S-T deviation has been set too low.

A remarkable effect of exercise on the electrocardiogram has been frequently noted in many types of heart disease, namely, a tendency for the abnormal T waves present at rest to become temporarily normal after exercise. This has been observed in patients with changes of left ventricular preponderance and in those with acute myocardial infarction patterns.[67] The mechanism and significance is unknown. However, they affect the practicality of the test very little, for the abnormal tracings at rest preclude the performance of the exercise test as a rule.

THE RELATION BETWEEN ELECTROCARDIOGRAPHIC CHANGES AND ANGINAL PAIN

The absence of any strict parallelism between the abnormal tracings induced by exercise and anginal pain has been appreciated for a long time.[67] Patients with slight pain may show marked electrocardiographic changes, while those with normal tracings after exercise may develop severe pain. Nitroglycerin given after exercise often quickly abolishes the pain while the changes in the electrocardiogram persist or even progress. Occasionally a positive exercise test is obtained in patients who do not experience any abnormal sensation during and after the exertion.[3,67,83] In other instances the tracing after exercise may be abnormal to the extent of showing the pattern of acute infarction temporarily; yet the patient may experience nothing more than a vague feeling of anxiety.[14,62] It has been noted that pain may not occur until five minutes after electrocardiographic changes developed after exercise.[64]

As a rule, however, in those patients who develop pain after exercise, the electrocardiogram is more often abnormal than in those who remain free of pain. Lenègre and Chevalla[40] found that eighty-two of ninety-two patients with positive tests experienced pain after exercise. Souliè and Joly found pain in thirty-nine out of forty-one positive tests.[40] On the other hand Wood and associates[83] noted a positive exercise test as frequently in those who developed no pain as in those who did.

THE USE OF EXERCISE TEST IN EVALUATION OF THERAPEUTIC EFFECTS OF DRUGS

Most of the drugs which are in use for therapy of angina pectoris have been investigated as to their effect on the outcome of the exercise test. It was soon established that nitroglycerin given shortly before the exercise will often lead to a negative test in patients who have a positive test without treatment.[3,67,68] The same observation has been reported for theophylline given intravenously before the test[63,68] and for khellin.[11]

The basis for this action is not well known. It is difficult to conceive that a vasodilatation caused by anoxia is further enhanced by drugs. Furthermore,

one should expect that the very high extraction of oxygen from coronary blood under normal conditions does not leave any reserve for an increased extraction in case of ischemia or hypoxia. Finally, it is obvious that the arteriosclerotic or syphilitic narrowing of the coronary artery is not diminished by nitroglycerin or other vasodilators.

Of interest are studies on the effect of digitalis on the exercise test. When digitalis was given to fifteen patients with coronary disease without congestive heart failure but with a positive exercise test, fourteen failed to show any change in the test or in the severity of the pain.[23] It was therefore concluded that digitalis did not appreciably influence the coronary circulation. When normal subjects were digitalized and then the exercise test performed, the changes noted were often similar to and as marked as those seen in coronary artery disease.[43,85] This does not necessarily mean that digitalis diminished the blood supply to the heart. Digitalis decreases the ventricular gradient. This action may summate with the decrease of gradient due to the exertional tachycardia and cause an "abnormal" S-T depression.

VALUE OF EXERCISE TEST FOR DIAGNOSIS OF CORONARY DISEASE

The exercise test is reserved for those instances where the diagnosis of coronary artery disease is suspected but is not definite. The experienced physician can establish a diagnosis in most cases of angina pectoris on the basis of a careful history. The therapeutic test of the administration of nitroglycerin often will help in those patients who do not have a typical angina on effort. There are instances, however, where the exercise test is of great assistance and of decisive value. It aids in the diagnosis of those patients who have had chest pain for only a short time and cannot correlate the pain with any activity or situation. The exercise test will aid in those patients with hiatus hernia or spondylarthrosis who experience pain only on walking. It will help reveal the presence of coronary ostium stenosis in patients with syphilitic aortitis who do not have pain on exertion but only a certain numbness or weakness in the arm. In general, it makes the diagnosis of coronary disease more objective whenever the history is unreliable. It will be of great help in connection with insurance examinations.[79] The exercise test is not performed routinely in all cases of coronary artery disease, nor should it be, because the element of danger cannot be completely eliminated. Clinically it is most useful in patients with an atypical history, negative clinical and electrocardiographic findings, and a doubtful outcome of the therapeutic nitroglycerin test.

Some of the earlier investigators found the test of little value because of the low frequency of positive results.[1,17,74] This may have been because too little exercise was used, because the tracings were not taken long enough after the exercise, or because the physiologic changes were confused with the pathologic ones. In an early study by one of us the test was positive in eleven out of twenty cases.[20] In a later study, with improvement of the technique the positive results rose to 80 per cent.[67] Similar results have been reported by others: Levan, 78 per cent[41]; Battro and Araya, 80 per cent[3]; Wood and associates, 88 per cent[83];

Kienle, 70 per cent.[34] Lower percentages of positive tests were reported by others: Twiss and Sokolow[78] found the test positive in 56 per cent of their series, Lenègre in 54 per cent,[40] and Soulié in 52 per cent.[40]

From this it is clear that a positive test strongly suggests the presence of coronary disease while a negative test does not exclude it. It is noteworthy that our percentage of positive results compares favorably with others, even though our criteria for abnormality are the strictest. At the same time we have eliminated for all practical purposes the error of false positives.

ACCIDENTS DURING PERFORMANCE OF TEST

Accidents are bound to occur when patients with coronary artery disease perform physical exercise. The very object of the test is to induce an inadequate blood supply to the heart muscle. Fortunately, if the precautions mentioned above are taken, the degree of ischemia does not become severe enough for permanent injury to result. In many thousands of tests over a period of more than twenty years, one of us has never had an accident. Others, however, have reported fatalities. Thus one death occurred during the test as reported by Faleiro[17]; but the observation was not made by him and details are lacking. One death was reported by Frey[19] and three by Rossier and Spühler.[58] The amount of work prescribed in these tests was almost double that recommended by us.

It is worth repeating that, in order to minimize the possibility of an accident, one should record and interpret a tracing immediately before the test in order to make sure that no infarction has occurred between the time the test was ordered and the time it was done. Also, the amount of exertion prescribed, at least for the first test, should be no more than that undertaken by the patient in his daily routine.

Of interest is the observation that administration of nitroglycerin often converts a positive exercise test into a negative one, but it does not influence the outcome of the anoxia test.[39]

FINAL REMARKS

In a great number of cases we had the opportunity to register, in the same patient, the electrocardiogram during attacks of angina pectoris, occurring at rest and after exercise. The electrocardiographic changes were identical in all instances.[61,66] Therefore one is justified in concluding that with an exercise test one induces the same changes in the heart muscle as those appearing during spontaneous attacks. The changes caused by exercise are the consequence of an increased demand of the myocardium because of increased work and higher rate. In the spontaneous attack coming at rest the increase of blood pressure and tachycardia, which are almost invariably found, are responsible. In addition an increased oxygen consumption by the heart because of an increased amount of circulating pressor amines may play a part. In some cases marked changes were observed in decubital angina without alteration of rate and blood pressure. In these patients the presence of a coronary spasm has been considered.[80]

Since it became known how frequently the electrocardiogram is altered during spontaneous attacks of angina pectoris or those induced by exercise, the theory that the anginal pain is caused by myocardial ischemia found wider acceptance. In this connection it is interesting to recall that the anginal pain induced by exercise may long have subsided, while the alterations in the electrocardiogram persist or even progress. This may be explained by the fact that the pain is due to accumulation of metabolites in the interstitial tissues while the electrocardiographic changes are caused by an abnormal status of the myocardial fibers.[64] In this connection experiments by Kountz and Hammouda are of interest[31]; they registered the electrocardiogram while the heart was perfused with "asphyctic" blood. The electrocardiographic changes were the same as those seen after ligation of a coronary artery. Perfusion of the heart with blood containing only abnormally high amounts of CO_2 or only abnormally low oxygen content caused different changes. These authors conclude that it is not the hypoxia of the tissues but the changes of the myocardial metabolism which are responsible for the changes in the electrocardiogram as seen in angina pectoris.

The diagnosis of "coronary insufficiency" in patients with a positive exercise test is permissible if it is understood that this term implies only the presence of a disproportion between demand and supply of blood. Unfortunately the term coronary insufficiency is widely employed as a definitive diagnosis at present without consideration of the fact that such divergent clinical syndromes as acute hemorrhage, carbon monoxide intoxication, coronary occlusion, pulmonary embolism, etc., may lead to hypoxia of the myocardium.

SUMMARY

The electrocardiographic exercise test is reviewed with special emphasis on its physiology. In order to evaluate better the pathologic changes, the normal post-exertional changes are discussed in detail. It is concluded that S-T deviations of less than 2 mm. after exercise should not be considered as definitely abnormal.

Based on the physiology of the changes of the coronary blood flow after exercise, it is concluded that the amount of exercise should not be prescribed according to the patient's age and weight. Rather, it should approximate the amount which is known from the patient's history to bring on symptoms. At the same time, for safety reasons, it should not exceed the amount which the patient voluntarily permits himself to do in his daily routine.

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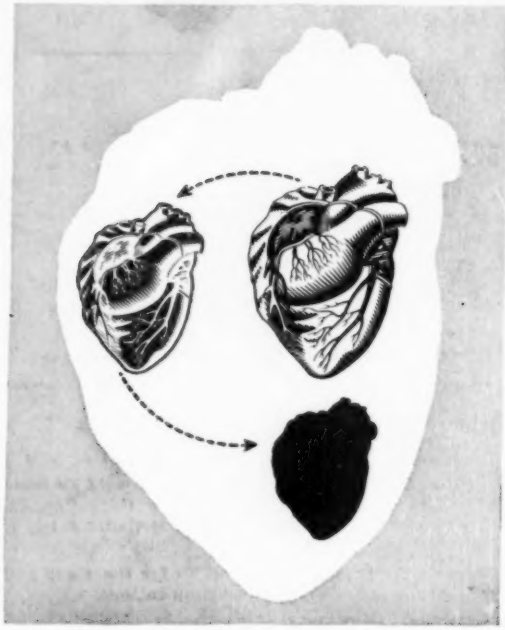

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